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Biomimetics As a Natural Alternative for Tooth Remineralization a Systematic Review

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ABSTRACT:

Dental enamel, primarily composed of hydroxyapatite nanocrystals, is susceptible to demineralization despite its formidable strength. Biomimetic remineralization, inspired by natural processes, offers promising non-invasive therapeutic avenues for restoring enamel. This review explores various biomimetic agents, including grape seed extract, Galla chinensis, propolis, Aloe vera, ginger & honey, theobromine, hesperidin, gum arabic, and tea polyphenols, highlighting their mechanisms and efficacy in promoting remineralization. Studies underscore the potential of these agents in enhancing enamel strength, inhibiting caries pathogens, and promoting remineralization. Despite challenges in clinical application and variations in research findings, biomimetic remineralization holds significant promise for revolutionizing preventive and restorative dentistry. The purpose of this paper is to provide a systematic review of knowledge about natural alternatives for tooth remineralization.

Keywords: ***Biomimetic remineralization, Dental enamel, Demineralization, Grape seed extract, Galla chinensis, Propolis, Aloe vera, Ginger & honey, Theobromine, Hesperidin, Gum arabic, Tea polyphenols.***

INTRODUCTION

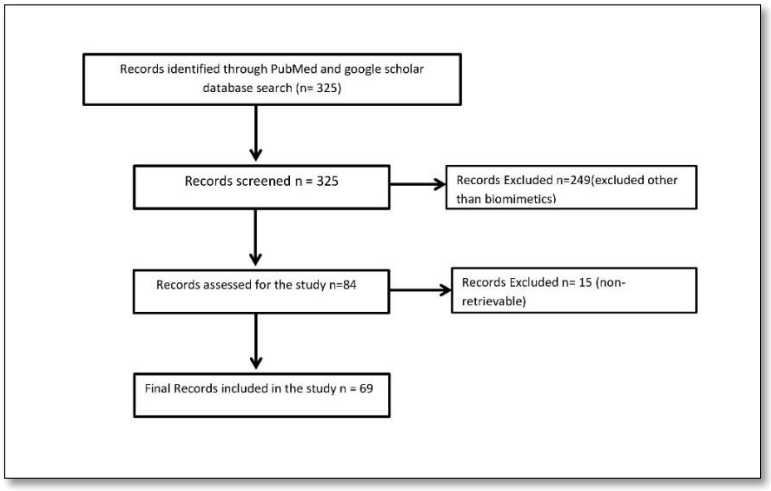
Dental enamel, a resilient tissue primarily composed of hydroxyapatite nanocrystals comprising 96% of its structure is formed by ameloblasts. These cells produce a protein matrix that mineralizes with calcium phosphate crystals, resulting in a cellular inert structure devoid of living cells. Despite lacking a specific color, enamel exhibits translucency, a visual effect arising from the intricate arrangement of hydroxyapatite crystals[1,2].

The formidable strength endowed by its high mineral content, notably hydroxyapatite, paradoxically renders enamel susceptible to demineralization.[3] The degradation of human dental enamel extends beyond mere aesthetics, profoundly impacting psychological well-being and overall health. Regrettably, as a non-living tissue, enamel lacks the inherent capacity for regeneration or remineralization, posing challenges for repair.[4]

Addressing enamel degradation, biomimetic remineralization has emerged as a non-invasive therapeutic avenue, seeking to restore dental tissues to their normal biological function and esthetics.[5,6] However, despite promising concepts, their clinical applications face limitations, often requiring intricate application conditions. The intricate nature of dental enamel underscores the challenges associated with its maintenance, prompting ongoing exploration of innovative solutions in dental research and technology.

The purpose of the current review aims to summarize literature to offer a concise and reliable overview of current research on biomimetic remineralization of enamel utilizing databases such as "PubMed," with strict inclusion criteria, focusing on original studies and reviews reported in English language literature while conference papers and posters were excluded(figure 1).

Fig 1: Flowchart of the study selection process



REVIEW

GRAPE SEED EXTRACT

Grape seed extract (GSE) has emerged as a promising substance for dental applications due to its rich content of polyphenolic compounds, particularly proanthocyanidins (PAs) derived from the seeds of Vitis vinifera. These components, including catechin, epicatechin, and epicatechin-3-O-gallate, contribute to GSE's antioxidant and antibacterial properties. Key findings suggest that GSE can enhance bond strength, reduce microleakage, and promote remineralization in dental restorations.[8,9] PAs in GSE play a crucial role in protecting dentine by strengthening collagen-based tissues, inhibiting enzymatic activity of glycosyltransferase F-ATPase and amylase and acting as collagen cross-linkers. Studies have demonstrated positive effects on the stiffness and

tensile strength of demineralized dentin. GSE might interact with proteins through various mechanisms, including covalent interaction, ionic interaction, hydrogen bonding interaction, and hydrophobic interaction.[10] GSE treatment concentrations varied between studies, which most often analyzed the impact of 5%, 6.5%, 10%, 12.5% or 15% GSE solution or gel but also employed comparison between them and with NaF, controls and etc. The total phenolic content was determined using the Folin– Ciocalteu method. Despite findings supporting GSE's benefit for stated use, conditions for treatment timing question its use in clinical practice. Often, GSE treatment conditions used in vitro were greater than 2 min and ranging upto 10mins for 2-6 weeks whereas one study showed usage of 10% gel for 1min. most of the studies have measured microhardness and few of them also measured modulus of elasticity testing and scanning electron microscope (SEM) imaging summarized in table 1. Most of the studies showed promising results with remineralization of enamel and dentin.

GALLA CHINENSIS

Galla chinensis (G. chinensis) is a traditional Chinese medicine derived from the abnormal growth of Rhus leaf tissue caused by parasitic aphids. It is rich in gallotannins, containing approximately 20% gallic acid (GA) and 7% methyl gallate. Through extensive research, including fractionation(adsorption chromatography with deionized water, 30% ethanol, 50% acetone and 100% acetone) and purification processes, GCE (Galla chinensis extract) has been identified as the most effective anticaries agent among various extracts(GCE-A, GCE-B, GCE-C and GCE-D were gotten. Further purification and fractionation of GCE-B resulted in the isolation of gallic acid (GA) and methyl gallate.). GCE has demonstrated the inhibition of caries pathogen growth, metabolism, and a positive influence on the demineralization/remineralization balance of enamel. Notably, GCE's efficacy surpasses that of other extracts, highlighting the significance of extraction methods in preserving bioactivity.[28,29]

Quality control is imperative for traditional Chinese medicine, leading to the selection of GCE, recognized for its potent effects, for further exploration. Previous studies have showcased GCE's impact on demineralization under dynamic pH-cycling conditions, its ability to enhance remineralization, and its synergistic effects with fluoride. Gallic acid and GCE exhibit distinct roles in enamel mineral deposition, with gallic acid primarily aiding surface layer mineralization, while GCE promotes deposition in the lesion body. The unique mechanism of G. chinensis, distinct from fluoride, regulates the demineralization/remineralization balance by influencing enamel crystal morphology, structure, and chemical content.[30] Table 2 provides a summary of studies comparing the effectiveness of GCE (Green Coffee Extract) with NaF (Sodium Fluoride) and deionized water as controls. The majority of these studies were conducted in vitro using extracted teeth models, with one study conducted in vivo. In the study conducted in vivo, participants in the study group were advised to use a toothpaste containing 2% GCE along with 1,450 ppm NaF twice daily for 2 minutes each time. The results showed a reduction in dentinal hypersensitivity, which was attributed to the sealing of dentinal tubules.

PROPOLIS

Propolis, stemming from Greek roots collected by bees from plant resins, carries significant potential in oral health due to its natural bioactive properties. Historically revered for its medicinal

qualities, propolis is rich in antioxidants, antimicrobial agents, and anti-inflammatory compounds. In dentistry, propolis has garnered attention for its diverse applications. Studies have highlighted its efficacy against oral pathogens like Streptococcus mutans and its ability to reduce inflammation and promote wound healing. Additionally, propolis has been investigated for use in various dental procedures.[43]However, research findings regarding propolis's impact on dental remineralization remain mixed. While Chen et al. (2015)[44] found that red propolis extracts effectively closed dentinal tubules, suggesting a positive impact on remineralization, Cardoso et al. (2016)[45] did not observe any inhibitory effects on caries demineralization with propolis ethanolic extract. The information summarized in Table 3 depicts the outcomes of several studies that have compared the impact of propolis with other agents on the remineralization process. Clarifying these discrepancies is essential for understanding propolis's true potential in promoting dental remineralization. Additional well-designed studies, incorporating various parameters and standardized methodologies, are needed to provide clearer insights into the efficacy of propolis

ALOE VERA

Aloe, the largest genus in the Xanthorrhoeaceae family, thrives primarily in arid climates across Africa, India, and other regions of the Old World. With approximately 140 species, Aloe plants boast a rich repository of phytochemicals, particularly concentrated in their leaves and gel. These compounds span a broad spectrum, including anthraquinones, anthrones, chromones, coumarins, pyrans, pyrones, alkaloids, benzene, naphthalene, and furan derivatives, flavonoids, sterols, tannins, polysaccharides, vitamins, and minerals.[53’54] This diverse phytochemical composition underlies the multifaceted biological activities observed in Aloe species. Traditionally, Aloe has been utilized for various health and medicinal purposes, prompting extensive scientific exploration into its pharmacological potential. Arginine, the predominant amino acid in Aloe vera gel, is joined by salicylic, uronic, and galacturonic acids, as well as sugars like fructose, mannose, and glucose. Enzymes such as oxidase, amylase, and catalase, alongside essential minerals like sodium, potassium, calcium, and magnesium, enrich its composition. Due to enamel's porous nature, Aloe vera dentifrices, comprising 35% gel, may foster remineralization by aiding arginine-calcium deposition. Acid exposure from bacterial metabolism can strip minerals from hydroxyapatite crystals, leading to increased surface porosity and opaque lesions, potentially reversible with remineralization.[55,56] Comparative studies on remineralisation using aloe vera have been tabulated in [Table-4]

GINGER & HONEY

Ginger (Zingiber officinale) is renowned in India for its antimicrobial and antifungal traits. Its rhizome oleoresin harbors bioactive compounds like 1-(4'-hydroxy-3'-methoxyphenyl)-5-hydroxy-3-deconone, noted for various physiological effects. Extracts like gingerol and shagelol from ginger exhibit antibacterial and antifungal properties.[60] The potential of ginger for remineralization is attributed to its antimicrobial actions and fluoride content. Recent studies have investigated ginger's role in non-invasive treatment for early caries lesions, leading to potential clinical benefits. Traditional Indian remedies often combine ginger with honey, known for its efficacy against oral pathogens. Honey is chemically composed of about 17-20% water, with its flavor and color contributing to its uniqueness. Its composition is complex, containing over 200 components, with sugar comprising 90-95% of its dry matter, alongside minerals and organic

acids. Manuka honey has been found effective in inhibiting plaque formation by preventing biofilm growth and reducing acid production. Honey's antibacterial properties stem from its low pH, high sugar content, hydrogen peroxide, low water activity, gluconic acid, and antimicrobial proteins/peptides. Manuka honey, in particular, contains phytochemicals like methylglyoxal and flavonoids, enhancing its antibacterial effects.[61] The ginger honey mixture was made by combining ginger powder with honey at a specific ratio. Studies demonstrated significant remineralization effects after using this mixture for a few weeks. Discrepancies in results could be due to differences in soil composition, water quality, and agricultural practices during cultivation. Table 5 outlines the findings from different studies that compare how ginger & Honey influences the process of remineralization

THEOBROMINE

Theobromine, a compound extracted from cocoa beans, has garnered attention for its potential role as a remineralizing agent for enamel. While historically chocolate consumption has been associated with a higher risk of dental caries, recent studies have highlighted the potential of theobromine as an effective remineralizing agent. As the primary alkaloid in cacao plants, its chemical name is 3,7-dimethylxanthine. Theobromine possesses antimicrobial properties, reducing the formation of Streptococcus mutans biofilms. Studies have explored its ability to increase crystallite size, potentially enhancing enamel strength.[65] It has also been found it to effectively occlude dentinal tubules within a short period when included in toothpaste formulations. One proposed mechanism of action is that theobromine may penetrate hydroxyapatite (HA) micro-tunnels, inducing internal stress that contributes to increased microhardness and has been linked to the formation of larger hydroxyapatite crystals, which can strengthen enamel and provide protection against acid attacks.[66] Table 6 provides a summary of research comparing the effects of theobromine on remineralization.

HESPERIDIN

Hesperidin, a flavonoid glycoside found in citrus fruits, is esteemed for its antimicrobial and remineralizing qualities. Initially isolated from citrus peel by French chemist Lebreton, it's also present in bergamot, lemon, banana, and other plants like leeks. Structurally, it consists of aglycones such as hesperetin or methyl eriodictyol bound to rutinose. Its versatility extends to treating diabetes, cancer, cardiovascular disease, and skin health.[76]

Studies indicate hesperidin's efficacy in remineralizing both superficial and subsurface lesions, possibly through collagen protein interactions. When incorporated into dental adhesive at specific ratios, it exhibits promising antibacterial effects without compromising adhesive properties. In clinical trials, hesperidin has been used to induce remineralization and halt active carious dentin due to its solubility in water.[77] This approach, backed by prior research, highlights the potential of natural substances like hesperidin in combating secondary caries. Overall, hesperidin emerges as a promising component in oral health interventions, harnessing its diverse properties for

therapeutic applications. Compiled comparisons of studies examining how Gum arabica impacts remineralization is summarized in [Table-7]

GUM ARABIC

Gum arabic, derived from Acacia trees, has a long-standing history of versatile applications, particularly in confectionery and diverse industries. Recent research highlights its potential as an antimicrobial agent against oral pathogens, aiding in plaque and decay prevention. Gum arabic acts as a prebiotic, supporting gastrointestinal health and potentially benefiting conditions such as chronic renal failure and diabetes. Moreover, gum arabic contains essential minerals like calcium, magnesium, and potassium, which are known to promote tooth remineralization. Specifically, the calcium ions present in gum arabic can replenish Ca2+ ions that have been depleted from hydroxyapatite crystals, thereby preventing further demineralization of enamel.[81,82] Research by Onishi T et al. has shown that the concentration of insoluble Ca2+ and PO4_ ions in gum arabic aids in facilitating tooth remineralization. Additionally, gum arabic exhibits the ability to inhibit acid-dependent demineralization and maintain remineralization even in fluoride-free environments. Incorporating gum arabic into oral care products, such as toothpaste, shows promising results in reducing plaque, gingival inflammation & demineralization, thereby supporting oral health maintenance.[83] With its diverse applications and multifaceted benefits, gum arabic emerges as a valuable natural resource for various health and industrial purposes, inviting further exploration and development in the realm of remineralization and oral care. Comparative studies on remineralisation using Gum arabica have been tabulated in [Table-8]

TEA POLYPHENOLS

Green tea, extracted from the Camellia sinensis plant, enjoys global popularity, with variants like green, black,white and Oolong widely consumed. However, green tea is particularly renowned for its health benefits.[84] Recent studies have emphasized its potential in cancer prevention, inflammation reduction, and brain health protection, largely due to its rich polyphenol content, notably epigallocatechin-3-gallate (EGCG). Tea leaves, containing polyphenols and fluoride, aid in combating dental caries. Catechins such as epicatechin (EC), epigallocatechin (EGC), epicatechingallate (ECG), and EGCG found in white and green teas act as MMP inhibitors. Furthermore, white tea exhibits antioxidant properties, counteracting oxidants.[85] Both green and white teas have been observed to protect demineralized enamel by enhancing surface microhardness and reducing enamel wear, owing to their high catechin content, thus enhancing enamel surface quality.[86] Information on the comparative studies investigating the remineralization effects of different tea's has been organized and presented in [Table 9].

CONCLUSION

In conclusion, biomimetics represents a promising approach in the remineralization of enamel and dentin, offering innovative solutions inspired by natural processes. By mimicking the complex structures and functions of biological systems, biomimetic strategies aim to enhance the natural remineralization process and restore the integrity of dental tissues. Most of them promote the formation of mineral deposits within demineralized enamel and dentin, effectively reversing early stages of tooth decay. As research in this field continues to advance, biomimetics holds great promise for revolutionizing preventive and restorative dentistry, providing effective and sustainable solutions for maintaining optimal oral health.

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TABLE 1: : **Summary and comparison of studies on remineralisation using grape seed extract.**

Sno.	Study	GSE concentration	Product comparasion	Treatment length	Parameters assesed	Study conclusion
1	Xie et al., 2008[9]	6.5% GSE	1000 ppm NaF Distilled water	10 min cycles 8 d	microhardness tester, polarized light microscopy (PLM) and confocal laser scanning microscopy (CLSM)	GSE inhibits the demineralization and/or promote the remineralization. The remineralization effect of GSE appears to be distinct from that of fluoride treatment.
2	Macedo et al., 2009[11]	6.5% GSE	No treatment, or 5% glutaraldehyde&glutaraldehyde + GSE	1 h	Microtensile Bond Strength Test (μTBS),Fracture Mode Analysis,Knoop Microhardness	Glutaraldehyde and grape seed extract significantly increased dentin collagen stability
3	Pavan et al., 2011[12]	6.5% GSE	1000 ppm NaF, distilled water, or NaF + GSE	10 min cycles 8 d	Mineral loss (ΔZ) and lesion depth (LD) by transverse microradiography.	GSE results in decreased rates of root demineralization
4	Benjamin et al., 2012[13]	6.5% GSE	220 ppm NaF 0.05% calcium glycerophosphate Control	10 min 6 cycles per dayr for 8 days	optical density	GSE revealed less demineralization and more remineralization compared with other groups
5	Tang et al., 2013[14]	5%, 10%, 15% GSE	controls	2 min, 14 d	Microhardness, X-ray diffraction analyses	A concentration-dependent increase was observed in the microhardness Field emission scanning electron microscopy revealed greater mineral deposition on their surfaces
6	Mirkarimi et al., 2013[15]	12.5% GSE	distilled water	10 min cycles 8 d	micro-hardness	GSE enhanced the remineralization process of artificial enamel lesions of primary teeth
7	Epasinghe et al., 2014[16]	Epasinghe et al., 2014	6.5% quercetin 6.5% naringrin	10 min 1 h 4 h	Tensile strength, modulus of elasticity (MOE)	proanthocyanidin>quercetin>naringin

8	Shi et al., 2015[17]	10% GSE	NaF, 10% GSE + NaF, distilled water	10 min 8 d cycles "	microhardness,Electron microscopy for dentin density	GSE and GSE +NAF showed significanty higher microharness
9	Silva et al., 2015[8]	6.5% GSE	1000 ppm NaF Distilled water	10 min cycles 8 d ¼	surface hardness and polarized light microscopy.	GSE inhibits demineralization of artificial carious lesions in both the enamel and dentin, but in a in a smaller scale when compared to fluoride
10	Rubel et al., 2016[18]	6.5% GSE	Normal saline	10 min cycles 8 d	micro-hardness	GSE group significantly increased the microhardness
11	Saragih et al., 2017[19]	6.5% and 12.5% GSE gel	artificial saliva	16 and 32 minutes and then immersed in artificial saliva for 6 hours at 37°C.	micro-hardness	revealed a significant increase in the enamel hardness value (p<0.05) after the application of the topical grapeseed extract gels at both concentrations. Application of 12.5% topical grapeseed extract gel for 32 minutes resulted in a restored hardness that insignificant diffrence from the initial hardness value obtained before demineralization
12	Jawale et al., 2017[20]	6.5% GSE	2.2 mM calcium glycerophosphate, 2.2 mM casein phosphopeptideamorphous calcium phosphate or distilled water	10 min cycles 8 d	polarized light microscope (PLM).	PLM data revealed a significantly thicker mineral precipitation band on the surface layer of the GSE-treated lesions compared to the other groups
13	Boteon et al., 2017[21]	10% GSE (gel)	10% cranberry extract 0.012% chlorhexidine 1.23% NaF Nothing (control)	1 min application (gel)	profilometry and hydroxyproline determination	Proanthocyanidin-enriched extracts were able to reduce the dentin wear and collagen degradation
14	Yassen and Safy, 2018[22]	15% GSE	1000 ppm NaF, artificial salvia	10 min 6/d, 8 d	microhardness,Electron microscopy for dentin density	significant increase in dentin micro-hardness values of GSE and NaF groups

			Control (no treatment)			
15	Nagi SM et al, 2019[23]	Grape seed extract 6%, 10%	fluoride 1.5 to 2mm thickness and left for 10 minutes on the labial surfa	1.5 to 2mm thickness and left for 10 minutes on the labial surface	Microhardness and energydispersive X-ray and ultramorphological examination	GSE hydrogels have positive effects on the remineralisation process.
16	Desai S et al., 2022[24]	not mentioned	Casein Phosphopeptide--Amarphous Calcium Phosphate (CPP-ACP), tricalcium phosphate	2hr/day, 10days	Scannng Electron Microscopy,(SEM), Energy Dispersive X-ray Analysis, (EDAX), and microhardness test	Grape Seed Extract (GSE) showed significantly greater remineralisation compared to the CPPACPF and tricalcium phosphate.
17	HM Hameed · 2023 [25]	6.5% GSE	1000 ppm NaF	6/d, 8days	microhardness test,Scannng Electron Microscopy,(SEM), Energy Dispersive X-ray Analysis,	Grape seed extract and NaF are equally effective in remineralizing surface
18	Ravi PV, 2023[26]	not mentioned	colophony. 5% NaF + colophony. grape seed extract + colophony. 5% NaF + colophony + 10% peptide. GSE + colophony + 10% peptide.	using a brushing stimulator for 3,000 cycleswith linear X, linear Y, and circular motion for every 1,000 cycles	microhardness test,Scannng Electron Microscopy,(SEM), Energy Dispersive X-ray Analysis,	Grape seed extract (GSE) with colophony and peptide is a superior natural alternative to NaF
19	Elgamily HM, 2023[27]	5 g of probiotic-3% GSE nanoemulsion-based jelly candy dissolved in 2 ml of saliva	nil	5mins 2/d for 15days	Vickers microhardness, atomic force microscopy (AFM), SEM, energy-dispersive X-ray spectroscopy (EDAX), and confocal laser scanning microscopy (CLSM)	probiotic jelly candy with potential remineralizing activity.

20	T. Almohareb et al.2024[10]	6.5 % GSE	odium ascorbate (SA), Green tea extract (GTE), Curcumin photosensitizer (CP) and Er: YAG laser	10mins	adhesive strength and marginal leakage	CP, GTE, and GSE improves bond values with a decrease in microleakage scores

TABLE: 2 **Summary and comparison of studies on remineralisation using Galla Chinensis**

Sno.	Study	GCE concentration	Product comparasion	Treatment length	Parameters assesed	Study conclusion
1	Abdel-Azem HM, 2020[31]	GCE (82% Rhus chinensis mill)	sodium fluoride, distilled water	two sub groups (1 min and 5 mins) for 12days	Energy Dispersive X-ray Analysis, (EDAX), and surface microhardness (SMH)	GCE groups showed no statistical significant difference in the 1-minute immersion & 5-minute immersion, both recorded higher mean SMH
2	Zhang et al., 2009[32,33,34,35]	4gL−1 GCE aqueous solution	1 g L−1 NaF, double deionized water	1MIN FOR 12 DAYS	a)transversal microradiography	G. chinensis inhibits enamel caries-like demineralization in vitro. However, its potential seems to be weaker compared to sodium fluoride
3					b)transverse microradiography	Galla chinensis can enhance the remineralization of initial enamel carious lesion, and the enamel organic matrix plays a significant role in this potential of Galla chinensis.
4					c)atomic force microscope	The surface roughness results provide the evidences to remineralization of carious lesion, and indicate the potential of G. chinensis in promoting the remineralization

5					d)Scanning electron microscopy equipped with energy dispersive analysis spectroscopy, X-ray microdiffraction (microzone XRD)	Natural G. chinensis may become one more promising agent for caries prevention
6	Zhang et al., 2010[36]	4gL−1 GCE aqueous solution	1 g L−1 NaF, double deionized water	1MIN FOR 12 DAYS	surface microhardness recovery (% SMHR) & scanning electron microscopy.	Galla chinensis enhances the remineralization of initial enamel carious lesions in vitro. The organic matrix of enamel was shown to play a substantial role
7	Huang XL, 2012[37]	4 g·L(-1) GCE solution,	4 g·L(-1) gallic acid (GA) sol, 1 g·L(-1) NaF sol(positive control), deionized water (DDW, negative control),	5mins/12cycles	liquid chromatography-time of flight-mass spectrometry (LC-TOF-MS) and quantified by high-performance liquid chromatography-diode array detector (HPLC-DAD).	GA showed an effect similar to GCE in inhibiting enamel demineralization (P>0.05).
8	Chu J, 2006[29]	4000ppm fourgroups GCE,GCEB, GCE B1 & GCEB2	1000ppm Faq. , deionized water	2H/day, 12 days	calcium of acid buffer was measured by American PE HTS 7000 plus & laser scanning confocal microscope.	potential of three GCEs (GCE, GCE-B and GCE-B1) to effect net rehardening of artificial carious lesions
9	Cheng L, 2010[38]	4000 ppm crude aqueous extract of GCE; 4000 ppm gallic acid	4000ppm F aq. , deionized water	2H/day, 12 days	scanning electron microscopy (SEM), energy-dispersive X-ray spectrometry (EDS) and X-ray microdiffraction (XRD)	GCE could affect the mineral ions deposit on the surface layer and mechanism seems to be different between GCE and gallic acid.

10	Guo B, 2012[39]	4 000 mg·L(-1) aqueous solutions of Galla chinensis extract	Remineralization solution (positive control), deionized water	21-h/4days 24h/3days	polarized light microscope	No significant difference between the Galla chinensis extract and the remineralization solution. So Galla chinensis extract has the potential to improve the remineralization
11	Zou et al., 2008[40]	4000 ppm aqueous solutions of five G. chinensis extracts (GCEs): GCE, GCE-A, GCE-B, GCE-C or GCE-D	4000ppm F aq. , deionized water	2x 5 min 12 times in 6 days.	Surface enamel Microhardness	The demineralization inhibition of GCE suggests that this material could be a useful source for the development of promising anti-cariogenic agents.
12	Xia Y et al., 2020[41]	2% GCE +1,450 ppm NaF Toothpaste	1,450 ppm NaF Toothpaste	Once in the morning and once in the evening, for 2 min each time for 4-8 weeks. Dental samples - 3min twice daily/7days	Scanning electron microscopy (SEM), and the degree of dentinal tubule plugging and diameter of the open dentinal tubules	Toothpaste that contained the active ingredients of *Galla chinensis* and sodium fluoride reduced the symptoms of dentin hypersensitivity by sealing the dentinal tubules.
13	Forcin LV et.al. 2021[42]	Toothpastes containing herbal compounds contained no fluoride [Galla chinensis (GCH)], low-F concentration [D'Or (DOR); Herbal Bliss (HBL)], or a different fluoride type [Elmex Anticaries (EAC)]	NaF-containing toothpastes: 1450 and 5000 ppm.	120 cycles per minute for 5mins for 7 days using Brushing Simulator Machine MEV-2T	surface hardness recovery (%SHR), the enamel surface roughness, pH, particle size, zeta potential, and polydispersity index	All toothpastes were able to remineralize the enamel

TABLE: 3 : **Summary and comparison of studies on remineralisation using propolis**

Sno.	Study	Product comparasion	Treatment length	Parameters assesed	Study conclusion
1	Zaleh AA et.al. 2022[46]	artificial saliva), 2% neutral sodium fluoride gel; NSF, Nano-curcumin (NCur), NPro, Diode laser irradiation (light), NCur with irradiation (NCur-PDT) and NPro plus NCur-PDT (NPro+NCur-PDT).	3 months	microhardness, surface changes, and surface topography of the enamel were examined using digital hardness tester, DIAGNOdent Pen Reading, and scanning electron microscope (SEM),	Combined use of NPro and NCur-PDT had more enamel remineralization efficacy in a shorter period
2	Anani H et.al. 2023[47]	control group; propolis group; hesperidin group; and silver diamine fluoride(SDF) group.	Radiographs taken at 6 week and 12 week followup	Digital X-rays were taken to assess remineralization	SDF, propolis and hesperidin agents showed promising effects in terms of remineralization
3	HosseinpourNader A et al., 2023[48]	Artificial saliva, sodium fluoride, propolis quantum dots, nisin, and quercetin nanoparticles		Surface changes, microhardness, and surface topography	Propolis quantum dots can be used for remineralisation of white spot lesions.

4	Midha V et.al. 2021[49]	four different pastes containing 5% NovaMin (Sensodyne Repair and Protect®), Propolis (Phytoshield Propolis®), 5% potassium nitrate (Sensodyne®), and 8% arginine (Colgate Sensitive Pro Relief®)	2min/twicedaily for 15 days	Scanning electron microscope	All materials, NovaMin, Propolis, potassium nitrate, and arginine, were effective in occluding dentinal tubules
5	Cardoso JG et.al. 2016[45]	with biofilm : propolis ethanolic extract (EEP), chlorhexidine digluconate 0.12%), ethanol 80%; and Milli-Q water without biofilm: EEP and Milli-Q water		percentage of hardness loss (%HL)	The EEP presented no inhibitory action on the de-remineralization of caries process.
6	Mohan AG et.al. 2014[50]	Acidulated phosphate fluoride (APF) gel, fluoride enhanced hydroxyapatite gel and propolis in conjunction with carbon-dioxide (CO2) laser		scanning electron microscopy and mineral changes by energy dispersion X-ray spectrophotometer	Laser irradiation of enamel through a topically applied APF gel is effective in the prophylaxis and management of dental caries.

7	Ali S et al., 2021[51]	Artificial oil and propolis oil	5,000 linear strokes,	Surface microhardness	Propolis has good remineralisation potential.
8	Gargouri W et al., 2020[52]	Xylitol, Xylitol+CPP_ACP, Xylitol+Propolis and artificial saliva	three times a day during 7 days	Mineral content by SEM and EDAX, surface morphology, microhardness	Xylitol with propolis showed dentinal tubules occlusion, improvement of microhardness, and decrease in roughness.

TABLE 4 **Summary and comparison of studies on Remineralisation using Aloe Vera.**

Sno.	Study	Product comparasion	Treatment length	Parameters assesed	Study conclusion
1	Al Haddad T et al., 2021[57]	1,450-ppm fluoride toothpaste; Aloe vera nonfluoridated toothpaste;AV 1,000-ppm fluoridated toothpaste; AV gel.	3mins/twice daily for 12days	scanning electron microscope—energy dispersive X-ray	The AV gel demonstrated a remineralization capacity equal to that of the 1,450-ppm fluoride toothpaste.
2	Yikici C, et.al. 2022[58]	Fluoride-free toothpaste, Fluoride Toothpaste with 1100 ppm fluoride, Fluoride Toothpaste with 1450 ppm fluoride, Aloe vera gel, Aloe vera gel+1100	2mins/twice daily for 14days	microhardness	toothpaste containing 1450 ppm fluoride and aloe vera provides an effective remineralization and sodium monofluorophosphate formulation may have a

		ppm Fluoride, Aloe vera gel+1450 ppm Fluoride			synergistic effect with aloe vera.
3	Silva TM et.al. 2016[59]	fluoride (Colgate Total 12) & Aloe vera (Forever Bright Aloe Vera Toothgel) dentifrice	10,000, 25,000, 50,000 and 100,000 brushing cycles (200 g load) in an automatic brushing machine with abrasive slurry	Knoop microhardness (KHN) analysis.	The toothpastes (containing fluoride or Aloe vera) were effective in increasing the superficial microhardness of artificial white spot lesions

TABLE 5 Summary and comparison of studies on remineralisation using Ginger, Honey and Choclate

Sno.	**Study**	**Product comparasion**	**Treatment length**	**Parameters assesed**	**Study conclusion**

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1	Kade KK et.al. 2022[62]	Control group,Remineralizing agent as fluoride toothpaste,Treatment material as ginger and honey paste & Treatment material as ozone oil.	1min/twice daily for 21days	surface microhardness & Surface roughness	There is no significant difference seen between each treatment group. Considering the adverse effect of fluoride, honey-ginger and ozone can be considered as good remineralizing agents.
2	Celik ZC, et.al. 2021[63]	Ginger ; Ginger-Honey-Chocolate ; Natural honey; Bitter chocolate ; MI Paste; Paradontax; Pronamel & Controls	1min(1:3w/w ratio with deionized water) for 5cycles along 7 days	surface microhardness &Fluorecam measurements	The herbals (ginger, honey, and bitter chocolate) examined in this study gave promising results with a high remineralization potential.
3	GB Gocmen et.al. 2016[64]	sodium fluoride toothpaste, ginger-honey, ginger-honey-chocolate, rosemary oil	1min/twice daily for 21days	Surface microhardness and fluorescence methods	Herbals (ginger, honey and rosemary) have enhanced remineralization of initial enamel lesion.

TABLE: 6 **Summary and comparison of studies on remineralisation using theobromine**

Sno.	Study	Product comparasion	Treatment length	Parameters assesed	Study conclusion
1	Taneja V et.al. 2019[67]	fluoridated dentifrice, Novamine, Nano-hydroxyapatite- Remin Pro,	14 days with two applications per day.	DIAGNOdent, scanning electron microscopy (SEM), and energy	All agents had remineralization potential; however, no significant difference was

		100mg and 5. 200mg of Theobromine toothpaste		dispersive X-ray (EDX) analysis.	found.Theobromine can be used as an effective novel remineralizing agent.
2	Premnath P et.al. 2019[66]	NaF + f-TCP, Amine fluoride, and Theobromine	1min/twice daily for 7days	Confocal laser scanning microscopy (CLSM)	theobromine demonstrated less remineralization potential in comparison to dentifrices containing NaF + f-(TCP) and amine fluoride.
3	Amaechi BT et.al. 2013[68]	artificial saliva; artificial saliva with theobromine (0.0011 mol/l) and NaF toothpaste slurry (0.0789 mol/l F)	2min/day for 28 days	scanning electron microscopy imaging and electron-dispersive spectroscopy (EDS) analysis, transverse microradiography (TMR) & surface microhardness (SMH)	theobromine in an apatite-forming medium can enhance the remineralization potential of the medium.
4	Thorn AK et.al. 2020[69]	fluoride (0.2 or 1ppm) and theobromine (0; 10; 100 or 200ppm) at different pH values (5.5 or 7.0)	for 24h	Knoop surface microhardness	Theobromine, when continuously present in a plaque fluid-like medium at various concentrations and at different pH values, does not affect de- or remineralization of enamel carious lesions

5	Farhad F et al., 2021[70]	artificial saliva,1.1 mol/L theobromine, and 0.05% sodium fluoride	1min before and after the remineralizing cycle for 7days	surface microhardness (SMH) test, and energy-dispersive X-ray spectroscopy (EDS).	Theobromine is an effective cariostatic agent, and can be considered as a safe alternative to fluoride in preventive dental care
6	Durhan MA et al., 2021[71]	fluoridated toothpaste. , theobromine containing toothpaste.	two times a day for 1 month.	Salivary pH, buffering capacity and frequency of Streptococcus mutans (SM) by Laser Fluorescence system	theobromine had the added benefits of increasing the salivary pH and decreasing the *S.mutans* levels, theobromine containing toothpastes can be considered effective agents in remineralizing white spot lesions
7	Golfeshan F et.al.,2021[72]	Theodent classic® toothpaste (theobromine); Power Energy toothpaste (caffeine); Colgate toothpaste (fluoride); and distilled water as the negative control	2 times a day for one month	surface microhardness	Theobromine toothpaste had the same remineralization effect as that of fluoride toothpaste
8	Farooq et.al. 2021[73]	Toothpaste+artificial saliva (AS): basic paste; basic paste+theobromine; commercial theobromine toothpaste; commercial BG	2 times a day for one month	Surface roughness	Treatment with toothpaste composition containing theobromine+F-BG resulted

		toothpaste; basic paste+fluoridated-bioactive glass(F-BG); and basic paste+theobromine+F-BG.			in the enamel's increased micro-hardness
9	Elmalawany LM et.al. 2023[65]	theobromine and casein phospho-peptides/amorphous calcium phosphate with fluoride (CPP-ACPF)	5min/1month	Scanning electron microscopy/energy-dispersive X-ray spectroscopy (SEM/EDX)	The pre-treatment of demineralized dentine with theobromine for 5 min or 1 month could enhance its bond strength and microhardness
10	Kargul B et.al. 2012[74]	one coat of theobromine at two concentrations (100 mg/l or 200 mg/l in distilled water) for 5 min & Control group	5min	Surface hardness and topography of human enamel.	Microhardness values, a consistent and remarkable protection of the enamel surface was found with the application of theobromine.
11	Damar S et.al. 2023[75]	calcium-phosphate compounds (CPP-ACP); TD, theobromine-containing toothpaste; RG, ROCS® remineralizing gel; L, Er,Cr:YSGG laser (2780 nm; 0.25 W; repetition rate, 20 Hz; pulse duration, 140 µs; tip diameter, 600 µm; without air/water cooling);	once/day for 8days	surface microhardness test, and scanning electron microscopy and microhardness recovery percentage (SMHR%)	Theobromine-containing toothpaste exhibited the least SMHR%. Long-term evaluation of these agents is recommended

		L + fluoride toothpaste; L + TM; L + TD; and L + RG.			

TABLE: 7 : **Summary and comparison of studies on Remineralisation using Hesperidin.**

Sno.	Study	Product comparasion	Treatment length	Parameters assesed	Study conclusion
1	Hiraishi N et.al. 2021[78]	hesperidin or chlorhexidine	2h for 8days	Atomic absorption spectrophotometer, assaying hydroxyproline & transverse microradiography.	Hesperidin preserved collagen and inhibited demineralization, and enhanced remineralization even under the fluoride-free condition.
2	Islam SM et.al. 2012[79]	hesperidin, chlorhexidine and grape seed extract	2h for 8days	Atomic absorption spectrophotometer, assaying hydroxyproline & transverse microradiography.	The hesperidin group showed the lowest value in lesion depth and mineral loss, indicating that hesperidin inhibited demineralization
3	Anani H et.al. 2023[80]	control group; propolis group; hesperidin group; and silver	Radiographs taken at 6 week and 12 week followup	Digital X-rays were taken to assess remineralization	SDF, propolis and hesperidin agents showed promising effects in terms of remineralization

		diamine fluoride(SDF) group.			

TABLE:8 : **Summary and comparison of studies on remineralisation using gumarabica**

Sno.	Study	Product comparasion	Treatment length	Parameters assesed	Study conclusion
1	Onishi Tet.al.2008[83]	10 mg/ml of gum arabic, sodium fluoride at 1000 ppm (NaF), or double distilled water	30mins/day for 7days	contact microradiographs	Gum arabic enhanced the remineralization of caries-like enamel lesions in vitro, suggesting its inhibitory effects towards dental caries.

TABLE: 9 : **Summary and comparison of studies on remineralisation using tea polyphenols**

Sno.	Study	Product comparasion	Treatment length	Parameters assesed	Study conclusion
1	He L et.al. 2015[87]	Nanosized calcium phosphate particles incorporating Tea polyphenols (TP) at	3 min/4times per day for 12 days	surface microhardness and transverse microradiography analysis	The novel nanosized TP-CaP particle, at low pH, is a potential dual-functional-remineralization and antibacteria-product

		different pH 7.0 and pH 5.5			
2	Jose P et.al. 2016[86]	Application of tea extract followed by CPP-ACFP (groups A & B) and CPP-ACFP followed by tea extracts (groups C & D)	for 21hrs	Vickers microhardness test	white tea can be considered as a viable option to functionally remineralize the demineralized dentine
3	Suyama E, 2011[88]	sugar-free chewing gum containing fluoride extracted from green tea and placebo gum	20 min/twice per day for four weeks	mineral change value (ΔZ, in vol%·μm).	FCG produced a superior level of remineralization and acid resistance, as compared to the placebo gum
4	Li JY,et.al.2004[89]	2000 mg/L tea polyphenol(TP), 200 mg/L TP, 2000 mg/L TP + 100 mg/L fluoride, 100 mg/L fluoride, and deionized water		microhardness	TP has no effect on de/remineralization of enamel blocks and there is no synergetic action of TP and fluoride in a sterile system.
5	Sarialioglu Gungor A, et.al.2021[90]	fluoride-free water, fluoride-containing mouthwash [Colgate Plax], green tea, rosehip, clove,	5-min/3 times per day over 5 days	Surface roughness, nanohardness values, and morphological changes	Clove and green tea extracts may present novel natural therapy potential by inhibiting dentin erosion.

		pomegranate, and grape seed)			
6	De Moraes MD et.al[91]	DW - distilled water, CHX - 0.2% chlorhexidine digluconate, and GT - green tea	5mins/3cycles for 3days	loss of surface hardness (%SHL) and mechanical profilometry analysis	The green tea extract solution was able to reduce the wear and roughness caused by dentin erosion
7	Hannas AR et.al.2016[92]	placebo, 1,100 ppm fluoride, 0.61% green tea extract, 0.12% chlorhexidine or 0.004% chlorhexidine (commercial toothpaste)	brushed for 15 s/day for 5days	Dentine tissue loss (µm)	toothpastes containing MMP inhibitors (0.12% or 0.004% chlorhexidine, or 0.61 % green tea extract) were able to prevent dentine wear caused by erosion and abrasion