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Bioinspired Dentin Biomodification: Current Evidence and Emerging Approaches

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Abstract: Dentin biomodification has emerged as a promising strategy to enhance the longevity and performance of adhesive restorations by stabilizing the collagen matrix and inhibiting enzymatic degradation. This literature review explores various physical, chemical, and biological approaches used to reinforce dentin structure and protect the hybrid layer from breakdown. The process of dentin biomodification primarily involves the use of cross-linking agents and matrix metalloproteinase (MMP) inhibitors to improve mechanical properties and reduce biodegradation of the exposed collagen network. Synthetic agents such as glutaraldehyde, chlorhexidine, and quaternary ammonium compounds demonstrate effective collagen stabilization but vary in biocompatibility. Natural agents, including proanthocyanidins, genipin, baicalein, and EGCG, offer safer alternatives with antioxidative and antimicrobial benefits. Recent advances in laser technologies, ultrasound, and nanohydroxyapatite have further expanded the scope of dentin biomodification by enhancing remineralization and promoting deeper interaction with the collagen matrix. These approaches collectively aim to improve the integrity of the resin–dentin interface and prolong the clinical lifespan of restorative treatments. While many agents show significant promise, further research is necessary to develop optimized bonding systems that integrate long-lasting biomodification and MMP-inhibitory functions in a clinically feasible manner. This review highlights the multifaceted potential of dentin biomodification in advancing restorative dentistry.

Keywords: *Dentin Biomodification; Collagen Cross-Linking; Matrix Metalloproteinase Inhibitors (MMPIs); Biomimetic Strategies; Adhesive Dentistry.*

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I. INTRODUCTION

Dentin is a mineralized tissue composed of intra-tubular and peri-tubular dentin, as well as tubules that run from the pulp to the DEJ. The organic matrix in dentin is composed of 90% fibrillar type I collagen and 10% non-collagenous proteins, such as proteoglycans and phosphor-proteins.[1] Dentin has an advantage over enamel because it has a scaffold made of collagen that offers a suitable, cell-free backbone for tissue regeneration and repair.

Dentin biomodification has recently been studied as a biomimetic approach therapy to modulate the rates at which extracellular matrix (ECM) components biodegrade and mechanically reinforce the current collagen network.[2]

The process of dentin biomodification entails using various cross-linking agents to stabilize dentin collagen. This procedure uses matrix metalloproteinase inhibitors (MMPI) to improve mechanical qualities and reduce enzymatic degradation.[3]

The durability of the so-called hybrid layer, which is made up of resin that penetrates the dentin's collagenous network, determines how long adhesive restorations last [4]. The hybrid layer is also primarily responsible for the bond strength of adhesion to dentin. Nevertheless, resin monomers do not fully penetrate collagen fibrils that are visible throughout the bonding process [5,6]. Unprotected collagen and porosities remain in the hybrid layer due to an incomplete penetration. This phenomenon, which has been called "nanoleakage," may eventually serve as a conduit for the breakdown of resin-dentin links. The acidic pH produced by bacterial metabolism may cause MMPs to become active and cause cathepsins to be released, which speeds up the breakdown of collagen close to the hybrid layer.[7]

The biomodification of the dentin substrate, which encourages collagen cross-linking to improve biomechanical qualities and reduce biodegradation rates, is an effective way to extend the longevity of adhesive restorations [2]. This process inhibits MMPs, lowers water permeability, and diminishes the molecular mobility of unprotected collagen [8].

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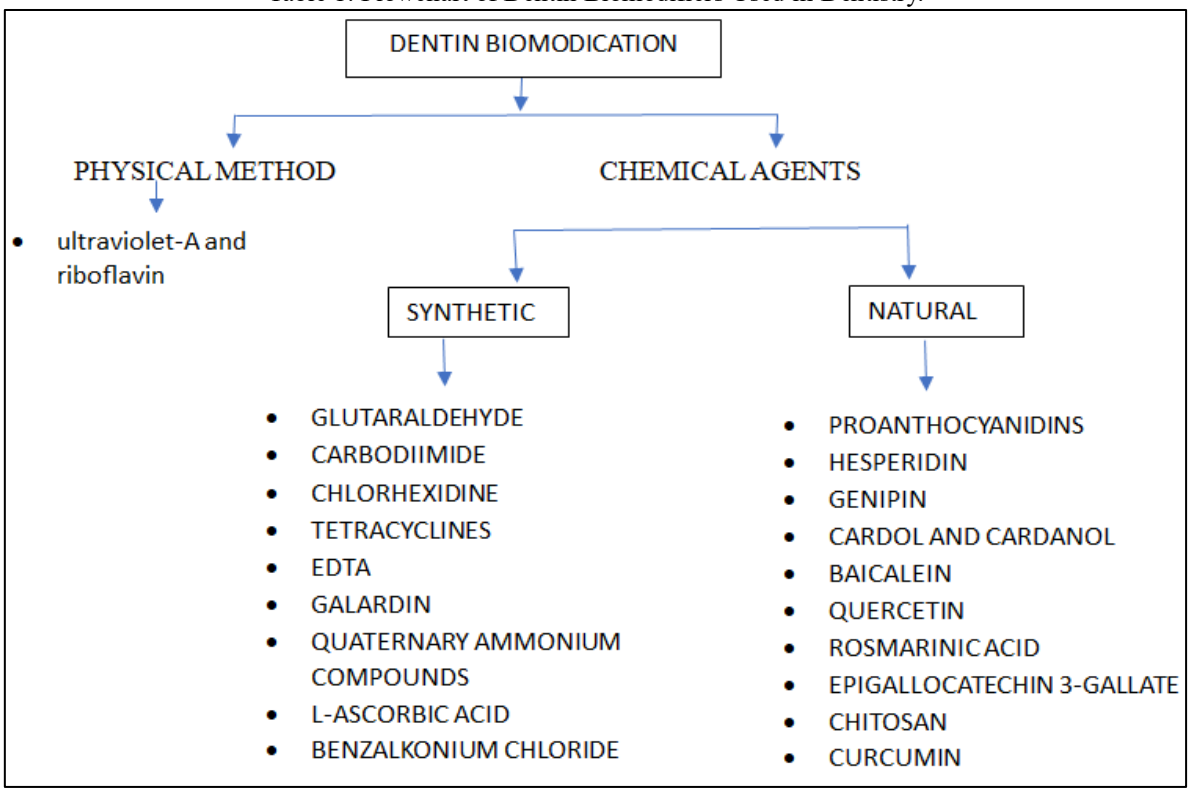
The present study aims to perform a literature review about the dentin biomodification agents used in dentistry.

Table 1: Flowchart of Dentin Biomodifiers Used in Dentistry.



II. PHYSICAL METHOD

The majority of artificial biomodifiers employ light exposure, particularly UV radiation, and are often referred to as the photo-oxidative approach.[9]

A water-soluble vitamin that is a part of the vitamin B2 complex is riboflavin (RF). In experimental restorative dentistry, it has been employed as a biomodification agent in combination with ultraviolet A (UVA) irradiation [2,10]. Collagen's inherent connections are broken by the high energy UVA radiation (365 nm wavelength), which also produces oxygen free radicals. Collagen's proline or lysine is attacked by hydroxyl functional clusters in RF. Furthermore, RF promotes the creation of new cross-links by acting as a photosensitizer for UVA. In addition to a notable increase in tensile strength, the application of RF/UVA enhanced resistance to collagen degradation caused by collagenase [11]. Visible blue light has been explored as a potential replacement for UVA light and has shown promise since it is more therapeutically useful and acceptable in dental clinics. [12,13]

Cova and associates further showed that RFP-induced crosslinking strengthens dentinal collagen's stability and makes it less vulnerable to matrix metalloproteinases' (MMPs') breakdown, specifically neutralizing MMP-9 [14]. According to Fawzy and colleagues, pre-treatment with RFP and UVA exposure resulted in a homogeneous hybrid layer with long, distinct resin tags in demineralized dentin, which supports these findings. [15,16]

III. CHEMICAL AGENTS

A. Synthetic

➢ Aldehydes

Although glutaraldehyde (GA) is the most well-known member of this family, other aldehydes including formaldehyde and glyceraldehyde also have a comparable capacity for cross-linking. GA is a dialdehyde that has a strong affinity for amino acid free primary amine groups [2,17]. The GA can form a cross-link with the collagen's lysine and hydroxylisine amino groups, increasing its tensile strength, flexibility, and resistance to degradation. However, its application in dentistry is limited due to its cytotoxic impact.[13]

➢ carbodiimide hydrochloride (EDC)

Because it may cross-link peptides without adding new linkage groups, carbodiimide hydrochloride (EDC) is referred to be a zero-length agent. The activation of the carboxylic acid groups of aspartic and glutamic acids results in the formation of an O-acylisourea intermediate, which mediates the cross-linking mechanism. Urea is the end result of the latter's reaction with the amino groups of lysine or hydroxylysine, which creates an amide cross-link. [2] Even after a 12-month water storage period, exposure to EDC has been demonstrated to dramatically raise the dentin's elastic modulus and slow down the rate at which collagen degrades.

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However, the length of the treatment up to one hour was clinically unfeasible. EDC exhibits lower cytotoxicity than GA because, the crosslinker's release urea derivative, which is readily washed off, leaving no chemicals behind.[18,19]

- Chlorhexidine [CHX]

CHX, a biguanide antimicrobial agent, has been broadly used in dentistry for its antimicrobial efficacy and substantivity [20]. It can be used to inhibit MMPs 2, 8, 9, without having a cytotoxic effect [13].

Chlorhexidine's cationic-anionic reaction with the glutamic acid residue of the cysteine domain is most likely the basis for its mode of MMP inhibition, which may distort MMP molecules and stop them from attaching to substrates [20,21]. Additionally, CHX may attach to MMPs and interact with calcium and zinc ions, which would reduce MMP's catalytic activity. It also binds to demineralized dentin electrostatically. This could be the reason for CHX's sustained MMP inhibition effectiveness in resin dentin bonding. In addition to adding CHX into primer and bond, 2wt% CHX has been incorporated into conventional phosphoric acid. It has been shown that the concentration of CHX affects the mechanical characteristics of bonding resin [20]. It has been demonstrated that 2% CHX, a traditional non-specific MMP inhibitor, is useful in preserving the strength of the resin–dentine bond strength following in vivo aging. [18,23]Since CHX digluconate is only accessible as an aqueous solution, adding adhesives to this solution could make the smear layer more water-entrapped [20,22]. Since CHX diacetate maintained the resin-dentin link and did not affect the water sorption, solubility, or conversion degree of adhesive systems, it has been employed in certain experiments in place of CHX digluconate [24,25,26].

- Tetracyclines

Broad-spectrum antibiotics like tetracyclines work well to manage periodontal infections. [27] They are regarded as MMP inhibitors with a broad spectrum. [20] Their capacity to chelate Ca+2 and Zn+2 [28] ions , necessary for MMPs to preserve their structure and functional active sites, was credited with their inhibitory actions. Consequently, tetracyclines can change the proenzyme (MMP) molecule's shape by attaching to the active site, and preventing its catalytic activity in the extracellular matrix. [20]

Tetracycline hydrochloride's characteristics include: Enhances fibronectin binding, which promotes the attachment and proliferation of fibroblasts. Removal of the smear layer, revealing the collagen fibers or dentin tubules, Dentin-binding endothelial cell growth factor, promotes the migration and proliferation of periodontal ligament cells. Absorbs to enamel and dentin, serves as a local delivery channel for antimicrobials and Collagenolytic enzyme inhibition[27]

- EDTA [Ethylenediaminetetraacetic acid]

EDTA functions as a chelating agent at neutral pH and has four carboxylic acid groups [24]. EDTA may suppress MMP activity because it is a powerful Zn2+ and Ca2+ chelator. By chelating the calcium and zinc ions from the enzyme that are essential for its optimal function, 17 %EDTA pretreatment of dentin beams for as little as one minute dramatically reduced the endogenous MMP activity of fully demineralized dentin beams.[20]

- Galardin

Galardin is a potent all-purpose synthetic MMP inhibitor of the hydroxamate type that works exclusively through Zn2+ chelation. MMP1, 2, 3, 8, and 9 are all strongly inhibited by galardin. It has been demonstrated that galardin lessens bond strength loss in a manner similar to that of CHX [20,29]. This inhibitor binds to the MMP active site more easily because of its collagen-like structure. Even when applied at a concentration of roughly 10 to 100 times lower (0.2 mM) for 30 seconds, it suppresses the proteolytic activity in the demineralized dentin in a manner comparable to CHX for a duration of 12 months.[24]

- Quaternary ammonium compound (QAM)

In contrast to the primary issues with chemically related quaternized monomers, QAM is a non-volatile and chemically stable polymer that is not permeable through the oral mucosa. Due to their antibacterial qualities and ability to copolymerize with adhesive monomers, polymerizable quaternary ammonium methacrylates (QAMs), particularly 12-methacryloyloxy dodecyl 1-pyridinium bromide (MDPB), have been used to self-etching primers. Both matrix-bound MMPs and soluble rhMMP-9 are inhibited by QAMs, such as MDPB [30].

In addition to killing bacteria, the cationic quaternary ammonium methacrylate (QAMs) can electrostatically bind to the negatively charged catalytic sites of MMPs, which contain cysteine-rich repeats, obstructing the active site. [20] Daood et al. [31] synthesized 2%, 5% and 10% quaternary ammonium silane (QAS) and showed that QAS inhibited endogenous MMPs and cysteine cathepsins. The 2% QAS is a good inhibitor of dentin proteases and could be an alternative for 2% CHX as MMPs inhibitor to improve the durability of the resin-dentin bond [24,32].

- L- Ascorbic Acid

Commonly referred to as vitamin C, L-ascorbic acid (AA) is a water-soluble, white to light-yellow vitamin. One of AA's salts is sodium ascorbate (SA). SA and AA both possess antioxidant qualities. When applied to dentin surfaces as an experimental conditioner, AA is known to improve the dentin bonding strength of adhesive resins [33]. In endodontic and operative dentistry, SA is known to improve the adhesive resins' ability to adhere to dentin surfaces that have been treated with sodium hypochlorite. [34]

- Benzalkonium chloride (BAC)

Benzalkonium chloride (BAC) is an antimicrobial agent containing a quaternary ammonium group. It has shown the ability to inhibit endogenous proteases [37]. It is sold commercially as an etchant (BAC 1.0 wt% phosphoric acid) with dubious outcomes [24]. Like biguanides, BACs can only be electrostatically linked to dentin collagen; as a result, they may leak out of the hybrid layer and lose their

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autoproteolytic properties. BAC levels of 0.5–1.0 % or above completely block rhMMP-2, 8, and 9 [35]. For 30 days, matrix-bound MMPs are inhibited between 55% and 76% by similar BAC concentrations. [20, 36]

B. Natural

➢ Proanthocyanidins (PAs)

A naturally occurring class of bioflavonoids, proanthocyanidins (PAs) are found in fruits, vegetables, nuts, seeds, flowers, and wood. [20] It is a member of a class of compounds called condensed tannins, which are heavily hydroxylated and can combine with proteins and carbohydrates to form an insoluble complex.[2]Flavan-3-ololigomers, which consist of three rings (ring A: triketide, ring B: phenyl propanoid, and ring C: condensation-formed pyran), are the building blocks of PAs. Catechin (C), epicatechin (EC), catechingallate (CG), and epicatechingallate (ECG) are the primary flavan-3-ol units found in grape seed extract PAs. Due to their physiological activities, which include anti-inflammatory, antimicrobial, and antioxidant qualities, effects on cardiovascular diseases, antiallergic effects, and enzyme inhibitory activities against phospholipase A2, cyclooxygenase, and lipooxygenase, have become more and more popular in the fields of nutrition, health, and medicine [38].

PA has been utilized as a natural collagen cross-linking agent in restorative and adhesive dentistry. Numerous investigations have demonstrated that PA stabilizes the dentin collagen matrix, enhances its mechanical characteristics, and increases its resilience to biodegradation [20,39, 40]. By biomodifying the demineralized dentin matrix with PA, the adhesive/dentin contact is stabilized against enzymatic degradation and proteolytic activity is inhibited. In order to increase the longevity of adhesive restorations, PA may be added to simpler hydrophilic adhesive systems. Liu et al. [41] showed that PAC-modulated dentin biomodification significantly reduces the collagenolytic and gelatinolytic activity in the demineralized dentin.[13]

➢ Hesperidin (HPN)

The glycoside flavonoid hesperidin (HPN), which is derived from citrus fruits, is a member of the flavanone subgroup. HPN's has many health benefits, including its anti-inflammatory, analgesic, anti-microbial, and antioxidant actions, are linked to its pharmacological characteristics and therapeutic applications. Additionally, HPN can prevent bone loss, block the proteolytic activities of MMPs, and limit carcinogenesis. Research demonstrated HPN's ability to shield collagen from proteolytic enzymes and that adding 2% HPN to a self-etch primer greatly increased the microtensile bond strength both immediately and after one-year storage period in artificial saliva. [20,41]

➢ Genipin (GNP)

Geniposide, which is isolated from Gardenia jasminoides Ellis fruit, hydrolyzes to produce Genipin. Collagen molecules main amine groups can react with GNP to create crosslinks. In tests on bovine dentine, GNP dramatically increases the collagen fibrils' resistance to enzymatic digestion in a way that is dependent on both concentration and duration [18, 42]. Moreover, the ultimate tensile strength and binding strength of adhesive restorations were significantly enhanced by the chemical alteration of human dentine with GNP.[43]However, because of aesthetic issues, its pigmentation effects may cause the treated dentine surface to become stained, which poses a clinical constraint [18,20] Because of its sluggish cross-linking reaction, its use is restricted. [2]

➢ Cashew Nutshell (CSNL)

Over 95% of the technical cashew nutshell liquid made in the industries is composed of cardol and cardanol. At low doses, cardanol, a non-cytotoxic substance with antioxidant qualities, exhibits inhibition of matrix metalloproteinase-2 and matrix metalloproteinase-9 [20]. They are a natural bio-modifier with a long 15-carbon alkyl side chain that interacts with the dentin substrate more hydrophobically and has a lower molecular weight than grape seed extract, which may penetrate the dentin collagen matrix more quickly and more thoroughly, improving the mechanical properties [1].

According to Moreira et al., using CNSL for one minute without coloring the dentin collagen produces the best biomodification results [44]. Cardanol and lignin in acid etchant enhanced hybrid layer protection against hydrolysis and MMPs by maintaining a stable bond strength with a comparatively high adhesive fracture pattern, as demonstrated by De-Paula et al. [8].

➢ Baicalein (BAI)

One of the main flavonoids found in Scutellaria baicalensis is baicalein (BAI). BAI can stabilize collagen fibrils and preserve the integrity of the hybrid layer in dentin bonding due to its possible MMP inhibition and cross-linking properties. BAI has the ability to function as a cross-linker because its hydroxyl groups can create hydrogen bonds with the amide carbonyl of proteins. [45]

Consequently, the following could be the MMP inhibitory mechanism of BAI in endogenous dentin-bond MMPs. First, by collecting metal ions like Zn2+ and competing with the enzyme's active core through a metal-chelating action, BAI may inhibit MMP activity. Second, BAI may cause MMPs to cross-link and change their molecular mobility or three-dimensional structure, which would impair their capacity to break down collagen. Third, BAI may use hydrogen bonds to crosslink with dentin collagen fibers, altering or obstructing the MMP recognition sites in collagen to prevent enzymatic complexation and coordination and shielding noncoated collagen from deterioration. [20] It efficiently increases the endurance of the resin-dentin bonding when used as a dentin preconditioner and then followed by an etch-and-rinse adhesive system. [24,45]

➢ Quercetin (QC)

As a member of the flavanol group, quercetin is frequently found in red wine, tea, onions, and apples. It has been demonstrated that QC improves the mechanical

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characteristics and thermal denaturation temperature of the extracellular matrix of heart valves due to its cross-linking capabilities. Quercetin offers several benefits, including anti-inflammatory, antioxidant and cancer preventing properties. MMP-2 and MMP-9 activity in PC-3 cells may be inhibited by quercetin [46]. It can cross-link with collagen to decrease the formation of water canals by resisting collagenase attack and strengthen its stability. Being a natural cross-linker, quercetin has been widely accepted for its biocompatibility and safety.

- Rosmarinic Acid

The diphenolic molecule rosmarinic acid (a-o-caffeoyl-3,4-dihydroxyphenyllactic acid) has two catechol (1,2-dyhydroxy-benzene) rings, which add to its polarity. In addition to its antioxidant properties, rosmarinic acid also has an MMP inhibitor action. The longevity of resin-dentin bonding may be increased by slowing the advancement of caries through inhibition of MMP-2 and -9 activity [47]. Because the cross-linked collagen matrix has better mechanical qualities and is more resistant to proteolytic degradation, a natural cross linker may strengthen dentin bonding. Additionally, rosmarinic acid has the benefit of having four phenolic hydrogens (-OH), which help to regulate the oxidation of free radicals. Because it scavenges reactive radicals, the -OH group in phenol functions as a chain-breaking antioxidant. [20]

- EGCG (Epigallocatechin-3-O-(3-O-methyl) gallate):

The strong inhibitory impact of EGCG on MMPs and cysteine cathepsins is concentration-dependent. First, by forming a novel conformation, EGCG binds to zinc ions, which are crucial in preventing collagen from degrading by shielding its cleavage sites from metalloproteinases. Second, it either masks the catalytic region of MMP-2 or exhibits hydrogen bonding and hydrophobic interactions with it, causing irreversible destruction of the MMP-2 molecule. The primary polyphenol component, EGCG, is present in over 50% of green tea. Researchers have attempted to chemically synthesize new function groups, such as acetylated, methylation, and glycosylated EGCG, to increase the stability and bioavailability of EGCG and give it new biological roles. When EGCG and EGCG-3Me were each incorporated into the adhesive, the resin-dentin interface was protected from thermocycling effects resulting in improved bonding. EGCG and EGCG-3Me modified adhesives showed effective antibacterial activity against S. mutans. Adhesive modification by EGCG-3Me at a concentration of 400μg/ mL may be a more promising method to improve the long-term use of resinous restorations [20,48].

- Chitosan

Naturally found in the cell walls of fungi, yeasts, insects, and primarily in the shells of crustaceans, chitosan is a biopolymer that is produced when chitin is deacetylated . It is a promising material that has potent antibacterial activity and is biocompatible, biodegradable, non-toxic, and bioadhesive. [49,50]By creating crosslinks with collagen fibrils, chitosan has been identified as a significant biomaterial that can strengthen the adhesive contact and prevent metalloproteinases from breaking down the dentin organic matrix [49]After coating dentin collagen with chitosan nanoparticles, chitosan demonstrated a notable increase in resistance to collagenase destruction .Additionally, it demonstrated an increase in the root dentin layer's microhardness.

As part of an etch-and-rinse adhesive, chitosan treated with methacrylate is suggested as a way to increase the longevity of dental restorations. [20] Isabella Ziotti et al.,showed that 2.5% chitosan solution improved the bond strength of the resin to dentin and did not negatively affect the chemical composition and morphology of the adhesive interface. Even after six months of deterioration, chitosan improved the restoration's mechanical resilience. [49]

According to a study by Panwar et al., CHNPs improve the mechanical stability and toughness of collagen as measured by Transmission Electron Microscopy. Additionally, it strengthens the collagen on the dentin surface's resistance to bacterial deterioration [16,51].

- Curcumin

The plant Curcuma longa's rhizome yields the well-known, non-toxic polyphenolic chemical curcumin. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the three main curcuminoids found in curcumin, which is isolated from natural extracts. Their capacity to chelate the catalytic Zn+2 ions necessary for MMP activity via curcumin's β-diketone zinc-binding site, which is comparable to that of tetracycline-based MMP inhibitors, explains how curcumin interacts with MMPs. The β-diketone form contains an activated carbon in the heptadienone linkage between the two phenolic rings. At acidic and neutral pHs (between pH: 3-7), the C-H bonds are weak on this carbon, and this allows curcumin to serve as a potent H donor.

Furthermore, proteins have the ability to release metal cations [52]. Curcuminoids aid in this process by chelating and eliminating metal ions from metalloproteins in slightly acidic environments. By crosslinking the collagen fibrils, curcuminoids can strengthen dentin collagen's resistance to degradation by endogenous protease. Curcumin and collagen interact through electrostatic charge interactions and hydrogen bonding. [20]

IV. RECENT ADVANCES

- Lasers

Laser technology has emerged as a promising tool for dentin biomodification, offering several advantages over traditional methods. Lasers can precisely target specific areas of dentin, minimizing damage to surrounding tissues. They can also be used to remove infected or decayed dentin while simultaneously sterilizing the area, reducing the risk of postoperative complications.

The Er:YAG laser is one of the most widely utilized lasers in dentin biomodification. The infrared energy emitted by this laser is easily absorbed by water. Because of this characteristic, the Er:YAG laser can remove dentin precisely

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while causing the least amount of harm to the pulp underneath. Additionally, it can be used to make micropores in dentin, which will improve the adhesion of dental restorations and increase the penetration of bonding materials.[53]

The diode laser is another kind of laser that has showed potential in dentin biomodification. Diode lasers can be utilized to promote tissue regeneration since they generate energy in the visible or near-infrared range. Low-level diode laser irradiation has been demonstrated in studies to stimulate the growth and differentiation of dental cells, including odontoblasts, which are in charge of the production of dentin.[54]

- Ultrasound

High intensity focused-ultrasound (HIFU) has promising potentials to be implemented in dentine-substrate biomodification [55]. It has been recognized that it affects biological tissues in a variety of ways . HIFU is high-amplitude ultrasound-energy that can be focused using a transducer on overlying tissue leading to changes created by high tensile waves via a cloud of bubbles. This leads to nonlinear acoustic effects forming a shock front necessary for producing the results [56-60].

Umer Daood et al., in the study reported that HIFU exposure, following treatment with hydroxyapatite (HA)-nanorods, the remineralisation potential of demineralized dentine surfaces improved significantly. This improvement was dependent on the duration of HIFU exposure, as demonstrated and validated by a number of characterization techniques used.

The more effective distribution and interaction of HA nanorods with the collagen fibrils of the demineralized dentine matrix may be the cause of this improvement in remineralisation potential. It is reported that HIFU generates a high intensity focused ultrasound waves using a focusing transducer with minimal damage to surrounding tissues that is primarily due to the formation cavitation bubbles [61] oscillating in a non-equilibrium state releasing high-speed jets after collapse releasing kinetic energy adjacently [62]. This generated stream of mechanical waves could be speculated to provide a mechanical advantage for the infiltration and delivery of HA nanorods within dentine collagen-matrix with subsequent interaction with collagen fibrils of demineralized dentine matrix.[56].A prior study by Mehta D et al.[63] shown the beneficial synergistic effect of high intensity ultrasound on the synthesis and production of hydroxyapatite.

- *Nanohydroxyapatite (nHAp)*

Because of its chemical and microstructural resemblance to human hydroxyapatite (HAp), the primary mineral component in dental biomaterials (dentin and enamel), nanohydroxyapatite is a synthetic bioactive inorganic material that finds extensive application in nanotechnology [64-66]. As a result, the best biocompatible and bioactive mineral substitute for demineralized dental tissue is nHAp. According to the study by Tattiana et al., the combination of nHAp and PA strengthens demineralized dentin in a different and efficient way because it can enhance collagen stability and encourage remineralisation in just one minute of treatment.[67]

V. CONCLUSION

Dentin biomodification offers a pathway to improve the longevity of dental restorations by addressing the inherent vulnerabilities of the resin-dentin interface. By employing agents that reinforce the collagen matrix and combat enzymatic degradation, this approach aims to minimize issues like microleakage and secondary caries, ultimately leading to more durable and successful dental outcomes. Recent advancements in laser technology and high-intensity focused ultrasound showed precise dentin treatment and enhanced remineralization. Furthermore, the application of nanohydroxyapatite, often in conjunction with natural cross-linking agents, presents a biomimetic strategy to strengthen demineralized dentin. However, further research is warranted to optimize their clinical application, assess long-term efficacy, and to evaluate potential side effects.

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