Review Article

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Strategies for Improving Hybrid Layer Durability in Restorative Dentistry: A Narrative Review of Dentin Biomodifiers

Abstract:

Objectives: To perform a true analysis of scholarly sources on various dentin biomodifiers used in dental adhesive advancements.

Methodology: A comprehensive search was performed for additional relevant literature to identify peer-reviewed articles. This focused mainly on the hierarchical structure of dentin, various biomodifiers, and studies exploring their dentinal applications.

Result: Dentin biomodifier strategies are broadly classified into synthetic and natural . Further these are divided into physical and chemical methods. All of these approaches demonstrate unique mechanisms of interaction with dentin tissue. While originally believed to rely solely on non-enzymatic collagen cross-linking induced by intra- or intermolecular collagen bonding for dentin biomodification. It is now understood that various correlation with other components of dentin are crucial for ensuring biomodification which prolongs the mechanical integrity and biological stability for dentinal bonding. Oligomeric proanthocyanidins (PAs) demonstrate strong bioactivity however their complex chemical composition requires a thorough analysis of key constituents to develop standardized, sustainable intervention materials prior to progressing to advanced clinical evaluation.

Essence: Gaining insight into dentin's hierarchical structure and the specific effects of therapeutic agents will support their application in enhancing the dentin-biomaterial interface and managing dental caries.

Key-words: Dentin biomodification, Collagen cross-linkers,Proanthocyanidin, Glutaraldehyde, Ethyldimethylaminopropyl carbodiimide, Anacardium, Riboflavin.

Introduction:

A better prognosis in restorative dentistry is defined by long-lasting restorations. However, substantial reports indicates that this goal is not consistently achieved, prompting extensive research efforts focused on enhancing the longevity of the resin-dentin bond.[1]

Modern adhesive systems adhere to dentin primarily through a micro mechanical process involving the creation of a hybrid layer, which forms at the collagen-resin interface, represents the weakest area of the resin bond interface, where stress often accumulates and failures are most likely to occur. While securing adhesion to enamel has proven itself as consistently robust over time, achieving durable adhesion to dentin remains a significant challenge.[2]

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The dentin forms the major part of the tooth[3]. Dentin is a highly mineral-content,resilient,off-white,lacking vascularization tissue surrounding the central pulp cavity. Fully developed dentin comprises roughly 70% mineral content, 20% organic constituents, and 10% water. Its mineral phase primarily consists of nano-sized hydroxyapatite crystals arranged in a plate-like configuration. The organic

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matrix is mainly made up of collagen, accounting for nearly 90% of its composition, predominantly type I collagen, accompanied by lesser amounts of types III and V, and sporadic inclusions of non-collagenous proteins and lipids.[4]

Type I collagen form the structural architecture , with non-collagenous proteins linking them perpendicularly. Among these non-collagen components of dentin matrix proteins, proteoglycans (PGs) are the most significant. Proteoglycans are composed of a core protein, glycosaminoglycans (GAGs), and link various proteins. They play a pivoting role in promoting dentin calcification and maintaining the structural stability of the collagen matrix.[5]

Modern restorative techniques typically rely on the penetration of synthetic resins from the bonding agents into the partially or completely demineralized collagen fibers that constitute the organic component of dentin.[6]

The durablity of the bond between resin and dentin tooth structure plays a critical part in ensuring the prolong-term clinical success rate of adhesives . Despite recent advances, the extended stability of resin-dentin interface remains unclear. Multiple elements have been associated with the detrioration of the resin to dentin bond adhesion. These include the inclusion of hydrophilic monomers in simplified adhesive systems, moisture levels in self-etching adhesives, incomplete penetration of resin into the hybrid layer, enzymatic disintegration of revealed collagen fibrils by naturally occurring collagen-degrading enzymes, elevated permeability of the bonded interface, phase instability within the hybrid layer, and suboptimal polymerization.[7]

The durability of hybrid layers relies on the stability of their key components, including collagen fibres and polymer chain. However, when collagen fibrils are exposed through acid etching, they are not fully infiltrated by resin monomers, limiting their protection against denaturation. As a result, unprotected collagen becomes more susceptible to creep and fatigue-induced rupture under repeated functional stress .[8] The retention of water in the hybrid layer results in monomer breakdown and deterioration of unprotected collagen fibers.[9]

Enhancing collagen's resistance to degradation may contribute to greater prolonged bond strength at the resin–dentin junction. This was the primary rationale behind introducing collagen cross-linkers into the bonding protocol. Collagen cross linkers help safeguard collagen fibrils from breakdown by improving their chemical structure and mechanical strength.[10]

However, collagen deterioration represents only one aspect of the overall biodegradation process, and the influence of collagen cross-linkers on the adhesive properties of the hybrid layer remains unclear. Some studies have shown that collagen cross-linkers can inhibit the polymerization of dimethacrylates, potentially reducing the degree of conversion within the hybrid layer and compromising bonding effectiveness.[11]

A novel approach in restorative dentistry involves the application of synthetic biomodification agents or natural compounds that promote cross-linking among collagen fibers.This cross-linking process enhances the biomechanical strength of dentin and contributes to reducing its susceptibility to biodegradation.Although promising, dentin biomodification remains relatively underrecognized among dental professionals.[9]

Table 1. Overview of Key Biomodifiers Utilized in Dentistry

Typesof Biomodification	**Biomodifiers**
Physical Methods	Riboflavinwithultravioletradiation
Chemical Agents	
→ Synthetics	Glutaraldehyde
	Carbodiimide
	Galardin
	Chlorhexidine
	Chitosan
	Curcumin
→ Naturals	Proanthocyanidin
	Hesperidin
	Genipin
	CardolandCardanol
	Epigallocatechin3-gallate
	Extractof the aroeira

Analytical Overview of Relevant Research:

Collagen cross-bridging, achieved through physical orchemical methods, has been suggested as an adjunct to adhesive procedures to enhance the architectural durablity of dentin collagen by forming inter and intramolecular bonds, thereby improving the endurance of the resin-dentin interface.[12] Table 1 highlights the principal biomodifiers applied in dental practice and will be discussed in this literature.

A. Physical Methods:

1. Riboflavin (RF), also known as 7,8-dimethyl-10-ribitylisoalloxazine, is a water-soluble vitamin from the B2 complex and serves as a well-established crosslinking agent in this method. When exposed to ultraviolet A (UVA) light, riboflavin transitions into an excited triplet state, producing reactive O^2species that promote the formation of a stable physical network within the collagen matrix. UVA-activated riboflavin has been demonstrated to enhance the mechanical strength of both demineralized and intact dentin.

When integrated into an experimental primer designed for dentin collagen crosslinking, it significantly boosts dentin bond strength while reducing nanoleakage at the interface and suppressing matrix metalloproteinase (MMP) activity in aged specimens. Although higher concentrations of riboflavin can shorten the application time to a more clinically acceptable level, they may cause increased yellowish discoloration of the dentin.

Additionally, concerns remain regarding therapeutic viability of UVA light sources, and the cytotoxic potential of riboflavin continues to be a subject of debate.[9]

It increase tensile strength range from 25–35 MPa (after photochemical crosslinking) with pH 7.0 having shelf life of 6-12months (Loguercio et al., 2015)

B. Chemical Agents:

Chemical biomodifiers may be further classify as synthetic or natural agents.

a) Synthetics:

1. Glutaraldehyde(GA):

GA is widely applied as a meshwork agent due to its low cost, high reactivity & high solubility in water solution.[13] GA can cross-links with the amino groups of collagen, specifically lysine and hydroxylysine, leading to increased tensile strength and elasticity, as well as reduced degradation.

Initial research by Maciel et al. showed that treatment with glutaraldehyde (GA) led to a permanent enhancement in the stiffness of dentin collagen. Subsequently, a commercially available GA-containing desensitizing agent—Gluma (Heraeus Kulzer GmbH, Germany), composed of 5.0% GA, 35% HEMA, and 60% water—was evaluated for its application in restorative dentistry.[14] Suppression of native human dentin MMP activity and enhanced durability of the adhesive bond were observed at the interfaces treated with Gluma.[15]

It significantly increases the elastic modulus and enhances dentin's ability to withstand bacterial collagenase deterioration. Notably, higher concentrations of GA, up to 25%, resulted in a faster increase in elastic modulus, while a 10% concentration provided better collagen declination resistance compared to the commonly used 5% concentration use as a primer in adhesive dentistry procedures.

Its use resulted in a marked improvement in tensile bond strength—an increase of 30–40 MPa as a dentin pretreatment with a pH of 3.5–4.0 and a shelf life of 12–24 months—independent of the type of adhesive solvent used (whether acetone- or ethanol-based) and the moisture state of the dentin (dry or moist) (Macedo et al., 2009).

It has also demonstrated efficacy in adhering to caries-affected dentin. Nevertheless, a short application time or insufficient interaction with the amino acid components of dentin collagen may lead to reduced bonding effectiveness. Glutaraldehyde (GA) is widely acknowledged for its ability to support collagen integrity by boosting structural properties and reducing collagen deterioration in living tissues.Despite these benefits, its well-documented cytotoxicity significantly restricts its use in dentistry.[14]

2. 1-Ethyl-3-(3 dimethylaminopropyl) carbodiimide and N-hydroxysuccinimide(EDC-NHS):

EDC has been used as a collagen cross-linking agent as a safer alternative to glutaraldehyde (GA) due to its lower cytotoxicity. Its action involves the non-specific activation of carboxyl groups in glutamic and aspartic acid residues, forming an O-acylisourea intermediate. This intermediate then reacts with the amino groups of lysine and hydroxylysine to create stable amide bonds. However, the activation process generally requires an application time of 1 to 4 hours, which limits its practicality in clinical settings.[16]

Cross-linking with EDC, especially in combination with NHS (N-hydroxysuccinimide), enhances resistance to enzymatic degradation, likely by masking cleavage sites targeted by bacterial collagenase. Additionally, EDC-NHS cross-linked collagen and collagen–gelatin microspheres have been used as delivery systems for bioactive compounds, including those derived from natural sources.Studies have shown that carbodiimide treatment can increase dentin bond strength to approximately 35–45 MPa at a near-neutral pH (6.7–7.0), with the aqueous solution remaining stable for up to six months (Bedran-Russo et al., 2010).[17]

A higher concentration of EDC was able to inactivate matrix-bound dentine proteinases and soluble recombinant human MMP-9 (rhMMP-9) with shorter treatment time such as 30–60 s.[18] The effect was found to be concentration-dependent to indirectly assess collagen stability, the thermal denaturation temperature of dentin collagen was measured after EDC treatment, with an increase in temperature indicating a more resilient and cross-linked collagen network.[14]

Table2 – Synthetic and naturally occurring crosslinking agents, including their chemical composition, solvent systems, active constituents, and manufacturing sources.[19].

Group	Composition	Solvent	Description	Manufacturer	Lot No.
GA1	1% Glutaraldehyde (v/v)	Distilled water	Protein crosslinker $OHC(CH_2)_3CHO$	Merck, Finland	S5334503-928
GA5	5% Glutaraldehyde (v/v)	Distilled water	Protein crosslinker $OHC(CH_2)_3CHO$	Merck, Finland	S5334503-928
GS1	1% Grape seed extract (w/v)	Hot water	Vitis vinifera, Natural proanthocyanidin source	Mega-natural gold grape seed extract CA, USA	13682503-01
GS5	5% Grape seed extract (w/v)	Hot water	Vitis vinifera, Natural proanthocyanidin source	Mega-natural gold grape seed extract CA, USA	13682503-01
R1	0.1% (–) Riboflavin (w/v)	Distilled water	Enzyme cofactor $C_{17}H_{20}N_4O_6$	Sigma–Aldrich, Finland	OSOM1704Y
R5	0.5% (–) Riboflavin (w/v) with UVA light 365 nm, 7 mW/cm²	Distilled water	Enzyme cofactor $C_{17}H_{20}N_4O_6$	Sigma–Aldrich, Finland	OSOM1704Y
S	10% Sumac (w/v)	Hot water	Rhus coriaria, Natural proanthocyanidin source	Collected natural seed	–
RP1	0.1% Riboflavin-5-phosphate (w/v) with UVA light 370 nm, 3 mW/cm²	Distilled water	$C_{17}H_{20}N_4P$	Sigma–Aldrich, Finland	24887210
CR20	20 µM Curcumin	0.2% Ethanol in distilled	(1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-	LKT LAB, USA	458-37-7

3. Galardin:

Galardin, a synthetic matrix metalloproteinase (MMP) inhibitor first described by Grobelny et al. in the 1990s, exhibits strong inhibitory activity against MMP-1, -2, -3, -8, and -9 due to its collagen-mimicking backbone that enhances binding to the MMP active site, and its hydroxamate functional group (R–CO–NH–OH), which effectively chelates the catalytic zinc ion within the enzyme's active domain.

It is also called by name as GM6001 or Ilomastat. It is evident that after treatment slowed the decline in bond strength and reduced nano leakage, but it did not completely prevent these effects. The decrease in bond strength observed in galardin-treated specimens may be attributed to the detrioration of resin components within the hybrid layers, caused by polymer engorgement and resin leaching following water or oral fluid absorption.

This leaching effect may be more pronounced during in vitro micro tensile testing, as a similar decrease in bond strength was noted with CHX in vitro , while in vivo studies showed complete inhibition of bond strength loss.[20]According to the study by Mazzoni et al., 2013, it has a pH of 6.8-7.2 and a shelf life of 6 months. It increases the tensile bond strength up to 32-38MPa.

4. Chitosan:

Chitosan, a biopolymer has gained attention for its ability to reduce collagen matrix degradation induced by metalloproteinases. It is derived from chitin, a copolymer sourced from the exoskeletons of crustaceans, fungi, and insects.[21]

It is a linear polysaccharide made up of randomly arranged (1→4)-linked units of 2-acetamido-2-deoxy-β-D-glucan (N-acetyl-D-glucosamine) and 2-amino-2-deoxy-β-D-glucan (D-glucosamine). This compound is obtained by treating chitin with an alkaline agent, such as sodium hydroxide.[22]

Chitosan is a cationic polysaccharide obtained by deacetylating chitin—a natural polymer found in the exoskeletons of crustaceans—through an alkaline treatment at elevated temperatures. Its use as a biomodifier agent has recently emerged as a focus of advancement in experimental adhesive dentistry.

Coating dentin collagen with chitosan nanoparticles (CNPs) resulted in a marked improvement in resistance to collagenase-induced degradation. Additionally, it led to an increase in the microhardness of the root dentin layer.[23]

Chitosan has been shown to increase tensile strength to approximately 32–40 MPa at a pH range of 5.0–6.5, with a shelf life of 6 to 12 months (Costa et al., 2020).

Furthermore, methacrylate-modified chitosan has been proposed as a component in etch-and-rinse adhesive systems to enhance the longevity of dental restorations. Additionally,

modifying dentin collagen with a defined ratio of chitosan and riboflavin helps stabilize the collagen fibrillar network, promotes resin infiltration, and supports the formation of a durable hybrid layer.[9]

In an in vitro experiment, dentin pretreatment with CNPs, regardless of concentration or application time, improved bond strength at the resin–dentin interface. Additionally, applying 0.2% CNPs for 60 seconds was found to stabilize the demineralized dentin against MMP-mediated collagen degradation while simultaneously enhancing the bonding performance of the self-etch adhesive to the dentin surface.[24]

5. Chlorhexidine(CHX):

CHX can inhibit matrix metalloproteinases (MMPs) 2, 8, and 9 without exhibiting cytotoxic effects.[25] Even at low concentrations (0.2%), it helps preserve bond strength and minimize degradation at the adhesive interface, as indicated by reduced nanoleakage. Its inhibitory action is attributed to the suppression of protease activity through calcium ion chelation. However, a major limitation of chlorhexidine is its low substantivity when applied to dentin.

Cavity Cleanser, a commonly used disinfectant, consists of an aqueous solution containing 2% chlorhexidine digluconate, meaning it is 98% water. When applied to the dentin, especially after acid etching, it could leave this surface overwetted. Taking this into consideration, the influence of chlorhexidine on adhesion could be more related to wetness control than to the intrinsic properties of this material.[9]

6. Curcumin:

Curcumin is a polyphenolic derivative from the plant *Curcuma longa* L. The natural extract of curcumin contains three primary curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin.[26]

Curcumin modulates matrix metalloproteinase (MMP) activity by chelating the catalytic Zn^{2+} ions critical for their function. This inhibition is mediated through its β-diketone moiety, which binds zinc in a manner akin to tetracycline-derived MMP inhibitors. The β-diketone group, located within the heptadienone bridge linking the two phenolic rings, contains an activated carbon due to electron delocalization between neighboring oxygen atoms. Under mildly acidic to neutral pH conditions (pH 3–7), the C–H bonds on this carbon become destabilized, allowing curcumin to serve as an efficient hydrogen donor. Furthermore, curcumin is capable of promoting the dissociation of metal ions from proteins.[27]

Under mildly acidic conditions, curcuminoids facilitate the chelation and removal of metal ions from metalloproteins. When applied to collagen, curcumin promotes collagen fibril aggregation in a concentration-dependent manner. Treatment of dentin collagen with curcuminoids enhances its resistance to degradation by endogenous proteases through the crosslinking of collagen fibrils. This interaction involves both hydrogen bonding and electrostatic forces. Additionally, curcumin has been shown to increase the resin–dentin bond strength to approximately 30–40 MPa within a pH range of 5.0–6.5, with a reported shelf life of 6 to 9 months (Paula et al., 2019).

Applying curcuminoids to demineralized dentin has been shown to suppress the activity of endogenous dentin MMPs and cathepsin K. Despite the study's limitations, these results indicate that curcuminoid compounds may be promising agents for minimizing collagen matrix breakdown.[28]

a) Naturals

1. Proanthocyanidin(PA)

Proanthocyanidins (PAs) are a group of naturally occurring bioflavonoids found in a variety of plant sources, including fruits, vegetables, nuts, seeds, flowers, and bark.[28] Several sources of proanthocyanidins (PACs) have already been investigated, including cocoa seeds (*Theobroma cacao*), tea leaves (*Camellia sinensis*), cinnamon bark (*Cinnamomum verum*), açaí fruit (*Euterpe precatoria*), and pine bark (*Pinus massoniana*). Among these, grape seed extract (*Vitis vinifera*) demonstrated the most favorable outcomes in dentin applications.[9]

Elementally, proanthocyanidins (PAs) are composed of flavan-3-ol oligomers that feature three distinct rings: ring A (a triketide unit), ring B (derived from a phenylpropanoid structure), and ring C (a pyran ring formed through condensation). Grape seed extract primarily contains flavan-3-ol compounds such as catechin (C), epicatechin (EC), catechin gallate (CG), and epicatechin gallate (ECG). Proanthocyanidins (PAs), the major bioactive constituents, have garnered significant attention in nutrition, health, and medical research due to their wide range of biological activities, including antioxidant, antimicrobial, and anti-inflammatory effects. They also play important roles in cardiovascular protection, anti-allergic mechanisms, and the inhibition of key enzymes such as phospholipase A2, cyclooxygenase, and lipoxygenase. [29]

Pas have been implimented in adhesive and restorative dentistry as natural agents for collagen cross-linking. Numerous studies have demonstrated that PAs help stabilize the dentin collagen matrix, improving its mechanical properties and increasing its resistance to biodegradation. Biomodifying demineralized dentin with PAs has been shown to inhibit proteolytic activity and strengthen the adhesive–dentin bond, making it more resistant to enzymatic degradation. As a result, incorporating PAs into simplified hydrophilic adhesive systems could be a promising approach to enhance the durability and longevity of dental adhesives.[30]

The use of proanthocyanidins (PACs) in dentin induces varying levels of collagen cross-linkage through non-enzymatic interactions, resulting in improved biomechanical properties and enhanced biostability. It also contribute to an increase in tensile strength, reaching up to 35-45 MPa, with a pH range of 4.5-5.5 and a shelf life of 6 months (Bedran-Russo et al., 2007), as well as an enhanced modulus of elasticity. Their strong affinity for proline-rich proteins facilitates immediate adhesion and stabilization of collagen fibers, even in demineralized dentin. Liu et al. demonstrated that PAC-induced biomodification of dentin significantly inhibits both collagenolytic and gelatinolytic activities in demineralized dentin.[9]

One of the research says that using CPP-ACPF(casein phosphopeptide amorphous calcium phosphate fluoride) following pre-treatment with plant-based dentin biomodifiercomponents containing proanthocyanidins (PA) may produce a collaborative effect on the remineralization of eroded dentin.[31]

2. Cashew Nutshell Liquid(Cardol& Cardanol)

Cardol and cardanol, extracted from cashew nutshell liquid (CNSL) of *Anacardium occidentale*, make up over 95% of its composition in industrial uses. The long 15-carbon alkyl side chains of these compounds facilitate enhanced hydrophobic interactions with dentin collagen fibrils, potentially aiding as one of the dentin biomodifiers. At low concentrations, both compounds are non-cytotoxic and exhibit antioxidant properties, along with inhibitory effects on matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9).[32]

The lower molecular weight of cashew nutshell liquid allows for deeper and faster penetration into the dentin collagen matrix, leading to a significant increase in bond strength (28–34 MPa). Moreira et al. reported that CNSL provides the best biomodification results when applied for one minute, without causing staining of the dentin collagen. It has a pH range of 6.0–7.0 and a shelf life of 9–12 months (Priyadarshan et al., 2014).

3. Quercetin:

Quercetin, a flavanol commonly found in foods like onions, apples, tea, and red wine, is known for its cross-linking properties. It has been shown to enhance the mechanical strength and thermal durablity of the extracellular matrix in heart valves. Quercetin also provides several health benefits, including anti-inflammatory, antioxidant, and anticancer effects. In PC-3 cells, it has been found to inhibit the activity of matrix metalloproteinases MMP-2 and MMP-9. Moreover, quercetin can cross-link with collagen, improving its stability by reducing water channel formation and protecting against collagenase-induced degradation. As a natural cross-linking agent, quercetin is widely recognized for its biocompatibility and safety.[30]

4. Epigallocatechin-3-gallate (EGCG):

Epigallocatechin gallate (EGCG), the primary polyphenol in green tea (*Camellia sinensis*), effectively inhibits matrix metalloproteinases MMP-2 and MMP-9. Beyond its ability to cross-link collagen, EGCG also demonstrates antimicrobial activity against both Gram-positive and Gram-negative bacteria. When applied as a 0.1% dentin pretreatment in conjunction with a conventional two-step adhesive system, EGCG helped maintain bond strength even after six months of water storage.[9] It increases resin dentin tensile bond strength upto 30-40MPa with a pH ranges from 5.5-6.0 with a shelf life of 6-9 months (Epasinghe et al., 2014).

5. Extract of the aroeira:

In contrast to the polyphenols from *Aroeira* (*Myracrodruonurundeuva*) and PACs, both reagents are individual molecules that can be chemically synthesized into dental monomers. This provides the opportunity to design collagen-binding and collagen-crosslinking monomers with significant potential for enhancing dentin bonding. However, additional research is needed to assess the long-term benefits of these Anacardiaceae-derived crosslinkers, as well as their biocompatibility with odontoblast-like cells.

When evaluated on dentin, they demonstrated augmentations in dentin's mechanical properties and resistance to detrioration.[33-34]

This study aims to evaluate the impact of cardol, cardanol, and aroeira extract as collagen crosslinking agents on the mechanical strength and degradation resistance of demineralized dentin, comparing their performance to that of proanthocyanidins (PACs) within a clinically relevant application timeframe. The underlying hypothesis is that cardol, cardanol, PACs, and Aroeira extract will yield comparable enhancements in the elastic modulus and mass stability of demineralized dentin.[35-38]

Conclusion:

Final Thoughts and Future Trends:

The origin of each crosslinking agent plays a significant role in its application method, clinical practicality, and accessibility. Riboflavin, a physical agent, poses industrial challenges in terms of large-scale production. In contrast, naturally derived plant-based extracts such as proanthocyanidins—found in tea leaves (*Camellia sinensis*), cinnamon bark (*Cinnamomum verum*), açaí fruit (*Euterpe precatoria*), pine bark (*Pinus massoniana*), and grape seeds (*Vitis vinifera*)—are more widely available and easily accessible in the market. Cardol and cardanol, extracted from cashew nut shell liquid (*Anacardium occidentale*), are industrial by-products, offering a sustainable and cost-efficient alternative for use in dental applications. Among other agents, curcumin offers easier extraction compared to chitosan, which is derived through the deacetylation of chitin—a polysaccharide found in crustacean exoskeletons—via an alkaline, high-temperature process. Synthetic agents such as glutaraldehyde present cytotoxic risks, whereas carbodiimide has emerged as a more biocompatible alternative due to its lower cytotoxic potential.

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