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RESEARCH ARTICLE

An Insight of Proanthocyanidin and Polyamidoamine-Calcium Phosphate Nanoparticles as Biomaterial Candidate for Dentin regeneration in Dental Pulp Capping: A Narrative Review

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ABSTRACT:
Dental caries is the world's biggest dental problem with an incidence of 95%, causing tooth demineralization and complications including pulp perforation and premature tooth loss. A non-toxic biomaterial is required for increasing dentine regeneration in reversible dental caries. Proanthocyanidin (PA) is grape seed-derived flavonoid as antibacterial, anti-inflammatory, and antioxidant. However, PA provides low bioavailability so that it can be combined with polyamidoamine-calcium phosphate (PAMAM-CP) nanoparticles as drug delivery system. The investigation of PA and PAMAM-CP nanoparticles paste-based as innovation biomaterial for dental pulp capping may potential to induce dentine regeneration. The aim of this narrative review is to describe the combination of PA and PAMAM-CP nanoparticles as dental pulp capping biomaterial for dentin regeneration in dental caries. PA is able to express runt related transcription factor (Runx2), bone morphogenic protein-2 (BMP2), osteocalcin (OCN), and dentine sialophospoprotein (DSPP) which increase biomineralization and odontogenic differentiation. PAMAM is a macromolecule that provides attachment to dentine and induces remineralization. CP nanoparticles are calcium phosphate-based drug carriers that facilitate dentinal tubules penetration. PA loaded PAMAM-CP nanoparticles would be encapsulated releasing PA. PA suppresses Nuclear Factor-kB signaling pathway activation and decrease tumor necrosis factor-α so that inhibit dentinal matrix degradation. PA increases Runx2 and DSPP expression that manifest in dental pulp stem cells differentiation into odontoblasts. Combination of PA and PAMAM-CP nanoparticles may potential and beneficial as pulp capping biomaterial for dentin regeneration in dental caries.

KEYWORDS: Proanthocyanidin, polyamidoamin, calcium phosphate, good health and well-being, pulp capping, medicine.

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INTRODUCTION:

Dental caries is the biggest dental problem in the world with an incidence of 95%.[1,2] Caries is a disease with a multifactorial etiology including host, agent, substrate, time and environment factors. Agent factors include the cariogenic bacteria such as *Scardovia wiggsiae, Streptococcus mutans, Streptococcus sanguinus, Actinomyces sp.,* and *Lactobacillus sp*. Microbial dysbiosis on the tooth surface and fermentation of carbohydrates to acid acts as substrate factors. The time factor affects the prolonged imbalance between demineralization and remineralization cycles of the tooth tissue. Environmental factors include the level of education regarding how to maintain oral health, socio-economics, and culture of a person or caregiver.[3-9] Caries lesions can occur on enamel, dentin, or both of them.[10] Demineralization of the dentin near the pulp at a distance of 0.5 mm to 1 mm causes a chronic inflammatory reaction in the subodontoblastic area. Untreated caries can lead to complications in the form of tooth loss.[11-13]

One of the innovative dentin remineralization agents from biomaterials is a combination of proanthocyanidin and polyamidoamine-calcium phosphate nanoparticles which is applied topically to pulp capping to induce dentinogenesis. Proanthocyanidin (PA) is the main bioactive compound from grape seeds as antibacterial, antioxidant, and anti-inflammatory.[14] Polyamidoamine (PAMAM) is a dendrimer with high nucleation capability as a biomineralizer of dental tissue.[15] Calcium phosphate (CP) nanoparticles are drug carriers combined with PAMAM to increase the strength of dental tissue and inhibit the development of caries. The combination of PA and PAMAM-CP nanoparticles as dental pulp capping material has the potential to regenerate dentin tissue in dental caries. Furthermore, the aim of this narrative review is to describe the combination of PA and PAMAM-CP nanoparticles as pulp capping biomaterial for dentin regeneration in dental caries.

Histology of Caries Lesions:

Caries is a chronic demineralization of dental tissue due to the interaction between host, agents, environment, and time. Caries is the metabolic activity of the colonization of *Streptococcus mutans* bacteria on the tooth surface with a supportive and persistent environmental condition for a long time. In 1980, Takao Fusayama released his team's study on the analysis of caries lesions at Tokyo Medical and Dental University.

The researchers were able to differentiate two layers in a caries lesion that were quite distinct in origin using histologic, biochemical, biomechanical, microscopic, and microbiologic methods.[16] Demineralized tooth lesions in the early stages can be stopped or is reversible. The low immunity of host and low salivary secretion also may increase the progression of dental caries.[17,18] Dental minerals consist of pure calcium phosphate-hydroxyapatite ions and can quickly dissolve when the pH level of the oral cavity decreases. The pH level of the oral cavity which is conditioned near to neutral contributes to the re-deposit of mineral ions in carious lesions, this activity is called remineralization.[19-21] One of the main remineralization agents is fluoride which is able to reduce the solubility of tooth minerals and increase the hydroxyapatite ion, thereby providing a strong caries prevention effect. The pH imbalance in the oral cavity that occurs continuously supports demineralization which results in the lesion developing and damaging the tooth structures including dentin, enamel, and perforation of the pulp chamber. At this stage, the caries lesion cannot be stopped or is irreversible. The treatment required are restoration, pulp capping, or tooth extraction based on case.[22,23]

Pulp Capping:

The open cavity that reaches the pulp vital conditions needs to be treated by administering medicaments to the pulp, which is called pulp capping.[24-27] Deep cavity if not treated results in loss of tooth vitality and decreased caries defense mechanisms, susceptibility to fracture, discoloration and decreased ability of regenerative therapy for complex pulp-dentin. The goal of the regeneration of the dentin-pulp tissue is to restore the physiological functions of the pulp such as sensibility, the ability to repair by mineralization and pulp immunity.[28]

There are 2 types of pulp capping, namely direct pulp capping and indirect pulp capping.[29] Direct pulp capping (DPC) is a primary dental treatment indicated after minor mechanical exposures of less than 1 mm.[30] DPC is performed on mechanically exposed healthy pulp by applying a biocompatible material to prevent leakage of bacteria and toxins in the exposed area while maintaining vitality and accelerating pulp healing.[31-33] Indications for DPC include minimal exposure of pulp and minimal bleeding in exposed pulp areas. Contraindications for DPC include pathological pulp conditions based on radiographs, a history of spontaneous pain, and bleeding in the pulp area.[34]

Indirect pulp capping (IPC) was performed on caries lesions that had approached the pulp chamber. The IPC method was carried out by removing all caries tissue except caries dentin with a soft consistency using an excavator to support the formation of reactionary dentine as a reaction from odontoblast cells which is considered as a physiological process. The process is continued by closing the cavity using biocompatible materials.[32] Indications for IPC are deep caries lesions near the pulp tissue, no tooth mobility, no history of spontaneous pain,

no pathological conditions in the pulp, and no alveolar bone resorption on radiographs. IPC contraindications include pathological pulp conditions based on radiographs, a history of spontaneous pain, mobility in the teeth, and alveolar bone resorption based on radiographic examination.[34,35]

Proanthocyanidin:

Proanthocyanidin (PA) is a natural flavonoid from the condensation of tannins contained in grape seeds (*Vitis spp*.) of 35.3 mg/g and as antioxidant, immunomodulatory, anti-bacterial, antiviral, anti-inflammatory, anti-allergy, and vasodilator agent.[36-38] The application of PA to the pulp facilitates increased expression and cross linking of dentin Collagen Type 1 A (COL1A1) and is biocompatible with the pulp. The expression of biomineralization, differentiating odontogenic regulators such as Runt-related transcription factor 2 (RUNX2), Bone Morphogenic Protein-2 (BMP2), Osteocalcin (OCN), and Dentin Sialophosphoprotein (DSPP).[39-41] Matrix deposition and biomineralization play an important role in the formation of new dentin. The exposed dental pulp cells treated natural biomaterial showed increased proliferation and expression of the genes required for extracellular matrix (ECM) formation.[42,43]

PA was obtained by extracting grape seed (*Vitis vinifera*) using ionic liquid as much as 0.2g of dried grape seed weighed in an extraction tube 15mL and 5mL IL added. The samples were processed in the vortex for 10 s and placed in a shaker for 4h of extraction, at room temperature. After that, the samples were centrifuged for 15 minutes at 5000rpm and the supernatant was obtained from the filtration process. The samples obtained after extraction will be analyzed by High Performance Liquid Chromatography (HPLC) and Thin Layer Chromatography (TLC) to identify PA compounds.[44]

Polyamidoamine:

Polyamidoamine (PAMAM) is a drug carrier of nano polymer composition capable of inducing tooth remineralization by absorbing Ca, P, and collagen matrix.[45] PAMAM is biocompatible, low toxicity, and immunomodulator.[46] PAMAM can attract Ca and P ions to induce remineralization. PAMAM is a macromolecular compound that can assist the regeneration of dentin. Immersion test in lactic acid for 14 days on control dentine showed demineralization and dentin with PAMAM administration showed that there was a decrease in demineralization in dentin. This is because the PAMAM macromolecules applied to demineralized dentin are able to bond Ca and P ions to form minerals in demineralized dentine so that remineralization occurs.[47]

The PAMAM synthesis method is carried out by preparing the nucleus of the initiator molecule which contains a functional group that can react as an active site in the initial reaction. The growth of the outer layer of PAMAM is accomplished by adding the amine-terminated surface to the methyl acrylate resulting in an ester-terminated outer layer and bonding with ethylene diamine to obtain a new amino-terminated surface. The ester-terminated (half generation) synthesis of PAMAM dendrimers was carried out using ethylene diamine which was dissolved in methanol then mixed and put in a refrigerator. Then a drop of methyl acrylate is added to the dendrimer solution. The resulting mixture was then stored at room temperature for several days at 45°C. The solution will then turn pale yellow and form the solid particles. The synthesis stage of the amino-terminated (complete generation) PAMAM dendrimers was obtained by dissolving ethylene diamine and multi-esters in methanol separately. The multi-ester solution is then cooled and gradually added to the ethylene diamine solution. The resulting mixture is then stored at room temperature for several days until a clear solution is obtained.[48]

Calcium Phosphate Nanoparticles:

Calcium phosphate (CP) nanoparticles are adhesive drug carriers with the ability to penetrate into the dentinal tubules.[49] CP nanoparticles release Ca and P ions and are able to neutralize acids quickly.[50,51] CP nanoparticles can induce remineralization and regeneration of dentin in pre-demineralization towards healthy dentin, neutralizes pH and can reduce biofilm production by bacteria.[15,52] CP nanoparticles have high bioactivity and cell adhesion and are biodegradable.[25]CP nanoparticles are synthesized through spray-drying techniques. Calcium carbonate and dicalcium phosphate solutions were dissolved into acetic acid solution to obtain Ca and P ion concentrations of 8 and 5.333mmol/L. The solution is then sprayed into a heated chamber to evaporate distilled water and volatile acid. The dry particles collected by electrostatic precipitators produced CP nanoparticles with an average particle size of 116 nm.[15]

Pa Loaded Pamam-Cp Nanoparticles as Pulp Capping:

Pathogenesis of dental caries is correlated with *S. wiggsiae* and *S. mutans* colonization during the early stages of eruption.[9,53] Active caries is able to reach superficial zone and subsuperficial porosity was proven to induce demineralization process. The progressivity of the disease is stimulated by biofilm formation followed by sclerotic dentin formation. Bacterial colonization produces an exopolymer matrix that plays an important role as the environment of bacterial growth manifests in increasing the caries lesions. Bacteria diffuse into the dentinal tubule then invade the coronal dentin area and

expand to the pulp.[32] The manifestation of caries lesion is an opened cavity which needs to be treated with indirect pulp capping when it reaches the pulp chamber.

The most common material for dental pulp capping is calcium hydroxide (CH) which is able to induce remineralization by activating ATPase enzyme to stimulate reparative dentin formation, acts as bactericidal agent and neutralise acid from hydrogen ion from cement.[34] Despite its advantages, CH has high solubility after application within 1-2 years. This later would manifest in the formation of tunnel defect below the restoration which is able to increase the probability of secondary infection and microleakage in the pulp area, so the secondary infection could occur persistently then induce pulp necrotizing process. This condition could reduce the clinical success of pulp capping treatment.[54]

A non-toxic natural biomaterial that induces dentin regeneration is a combination of PA and PAMAM-CP nanoparticles. This combination is able to increase dentin mineralisation, anticariogenic, and consistently neutralise pH.[55] The pH neutralise ability of this combination potentially suppresses nanoleakage risk due to bacterial metabolism, enzyme, and oral cavity liquid. Besides, the nano-sized PA and PAMAM-CP is able to penetrate into the dentinal tubule. Dentinal bonding with PA and PAMAM-CP nanoparticles through electrostatic interaction as the primary component of remineralization in an oral fluid-flowing environment. This condition could increase adhesive property between dentin and materials also high seal adaptation to regenerate dentin tissue which is able to increase the success of pulp capping.[47]

Combination of PA *loaded* PAMAM-CP *nanoparticles* would be encapsulated releasing PA. PA suppresses macrophages activation and increases miR-506 expression so Toll Like Receptor-4 (TLR4) signalling pathway activation is inhibited. TLR4 signalling pathway is activated by lipopolysaccharide (LPS) from bacteria found in pulpitis and profunda caries. The blockage of this pathway suppresses MyD88, NOD2, Rip2 expression then disrupts the activation of caspase-1 and NF-kB *signalling pathway* manifest in decrease in Interleukin (IL) IL-1β/6, Tumor Necrosis Factor-α (TNF-α), p53, and p21 expression. This condition followed by disruption of cathepsin B and K and suppression of MMP-2/9 expression so the destruction process of the dentin and pulp is inhibited.[56-68]
PA induces COL1A1 formation and cross-linking to dentin. COL1A1 is an organic material of dentin matrix. The cross-linking and density of COL1A1 was increased by adding the dose and reaching the highest point in 15% PA. Induction of COL1A1 expression is a manifestation of BMP-2 expression then activates the ERK1/2-Smad2/3/4 signaling pathway so importin 7 (IPO7) is elevated. IPO7 later induces HtrA1 expression manifests in Transforming Growth Factor-β1 (TGF-β1) expression. TGF-β1 is a growth factor that plays an important role in odontogenic differentiation and cell proliferation. TGF-β1 induces COL1A1 and Tissue Inhibitor Metalloproteinase-2 (TIMP-2) so the formation of dentin matrix is increased. This process followed by angiogenesis induction after Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor-2 (FGF-2) expression through TGF-β1 expression facilitate nutrition and oxygen supply then increase the cell proliferation rate as the marker of optimum regeneration of dentin and pulp. The expression of TGF-β1 and activation of H19/SAHH signalling pathway could induce the expression of OCN, RUNX2, and Distal-Less Homeobox 3 (DLX3) then DSPP is elevated.[69-79] DSPP followed by release of calcium (Ca^{2+}) and phosphate (PO_4^{3-}) by PAMAM-CP nanoparticles fragment facilitate PAMAM fixation to the ions to form hydroxyapatite. The increase in extracellular Ca^{2+} induces the formation of Dentin matrix protein 1 and its receptor, Glucose regulated protein-78 (DMP1-GRP78) complex and FGF2 expression, then induces interaction between Calcium release-activated calcium channel protein 1(Orai1) and stromal interaction molecule-1 (STIM1) to activate the store-operated Ca 2+ entry (SOCE) signaling pathway. This followed by Runx2 expression then induce Osterix (OSX), Wnt3a. RUNX2 expression manifests in odontoblast and odontoblast-like cell differentiation also increase dentinal tubule calcification.[80-89] Combination of PA and PAMAM-CP nanoparticles as pulp capping biomaterial is able to inhibit caries progression, neutralize acidic condition from biofilm, and strengthen the tooth structure.[47]

CONCLUSION:

Based on our narrative review, combination of PA and PAMAM-CP nanoparticles may potential and beneficial as pulp capping biomaterial for dentin regeneration in dental caries. Further research is needed regarding the combination of proanthocyanidin and polyamidoamine-calcium phosphate nanoparticles as pulp capping biomaterials in regenerating dentin tissue.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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