

Narrative Review

Clinical applications of self-assembling peptides in dentistry: Enamel remineralization, dentin repair, and tissue regeneration

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ABSTRACT

Dental caries is a dynamic process driven by an imbalance between demineralization and remineralization, traditionally managed by invasive restorative methods that sacrifice healthy tooth structure. The shift toward minimally invasive and regenerative dentistry has promoted interest in biomimetic materials, particularly self-assembling peptides (SAPs). P11-4 and RADA16 are among the most widely investigated peptides, capable of undergoing pH-triggered self-assembly into β -sheet nanofibers that form a three-dimensional hydrogel scaffold. This matrix acts as a template for hydroxyapatite nucleation, promoting guided enamel remineralization. Evidence demonstrates that P11-4 effectively regenerates early enamel lesions, including post-orthodontic white-spot lesions, with superior remineralization efficacy compared to fluoride and without compromising bracket bond strength. SAP-mediated biomineralization also shows potential in managing dentinal hypersensitivity through intratubular crystal deposition, as well as emerging applications in bone regeneration and pulp revascularization, supported by favorable biocompatibility and scaffold characteristics. However, challenges persist regarding stability, standardization of peptide design, and sensitivity of self-assembly to environmental conditions. This narrative review summarizes the mechanisms, applications, and limitations of SAPs in dentistry.

Keywords: Biomimetic dentistry, Dental applications, Enamel remineralization, P11-4, Self-assembling peptides

INTRODUCTION

Caries results from an imbalance between demineralization and remineralization, leading to progressive mineral loss and, eventually, tooth decay (cavitation). Traditional treatment involves drilling and filling, which replaces lost tissue with restorative materials but is invasive and sacrifices sound tooth structure. To avoid or delay such interventions, various non-invasive and minimally invasive strategies have been introduced for early, non-cavitated lesions.^[1]

With the growing shift from reparative to regenerative dentistry, regenerative medicine-based approaches that aim

to replace damaged tissues with biologically similar structures are gaining importance.^[2] Among these innovations, P11-4 is a rationally designed self-assembling peptide (SAP) that forms fibrillar scaffolds under specific environmental conditions. It initially assembles into one-dimensional nanotapes that further organize into ribbons and fibrils through intermolecular hydrogen bonding and side-chain interactions, resulting in a versatile class of self-assembling peptides (SAPs) with potential applications in hard and soft tissue regeneration.^[3]

Interest in SAPs has grown substantially in recent years, driven by their promising applications in biomaterials, nanomedicine,

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nanomaterials, and nanobiotechnology.^[4] Among them, the ionic-complementary peptide P11-4 has attracted particular attention due to its pH-triggered self-assembly into β -sheet nanofibers, which form a three-dimensional hydrogel within demineralized enamel microporosities.^[5,6] This scaffold concentrates calcium and phosphate ions, guides hydroxyapatite nucleation, and supports subsurface remineralization of early enamel lesions.^[3]

Search strategy

This narrative review was based on a comprehensive, non-systematic literature search conducted to identify relevant evidence regarding self-assembling peptides and their applications in enamel and dentin remineralization. Electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science, were searched for articles published between January 2000 and January 2025.

Search terms included combinations of the keywords: “self-assembling peptide,” “P11-4,” “RADA16,” “biomimetic remineralization,” “enamel regeneration,” “dentin remineralization,” “collagen mineralization,” “biomineralization,” and “early caries lesions.” Additional articles were identified through manual screening of reference lists of relevant publications.

Peer-reviewed original research articles (in vitro, in vivo, in situ, and clinical studies) as well as relevant review articles published in English were considered. Studies not directly related to dental hard tissue applications were excluded. The selected literature was analyzed and synthesized to provide a comprehensive overview of current evidence and emerging perspectives.

Discovery of self-assembling peptide

The use of peptides as structural materials originated from an accidental discovery. In 1989, researchers at the Massachusetts Institute of Technology identified a SAP segment within a yeast protein. This repetitive sequence, named EAK16 (n-AEAEAKAKAEAEAKAK-c), forms an α -helical structure, with ionic interactions occurring between the glutamic acid and lysine side chains.^[7]

Structure of self-assembling peptide

Protein structure refers to a polymer of amino acids linked by peptide bonds, where the specific sequence of amino acids determines the type of protein formed—any change in sequence can alter its conformation. Protein architecture is organized into four levels. The primary structure consists of amino acids containing amine and carboxyl groups, along with various side groups such as thiols and alcohols, which enable diverse chemical interactions and molecular recognition. Alternate carbonyl and amine groups facilitate hydrogen bonding, leading to the formation of secondary

structures. The secondary structure depends on the primary sequence and includes stable arrangements, such as α -helices and β -sheets, while irregular coils, loops, and turns represent less stable forms. These secondary units fold further to form tertiary structures. The tertiary structure arises through interactions maintained primarily by non-covalent forces such as hydrogen bonding, electrostatic interactions, and aromatic stacking. Finally, the quaternary structure is formed when two or more polypeptide chains combine to function as a multi-subunit protein^[8] [Figure 1].

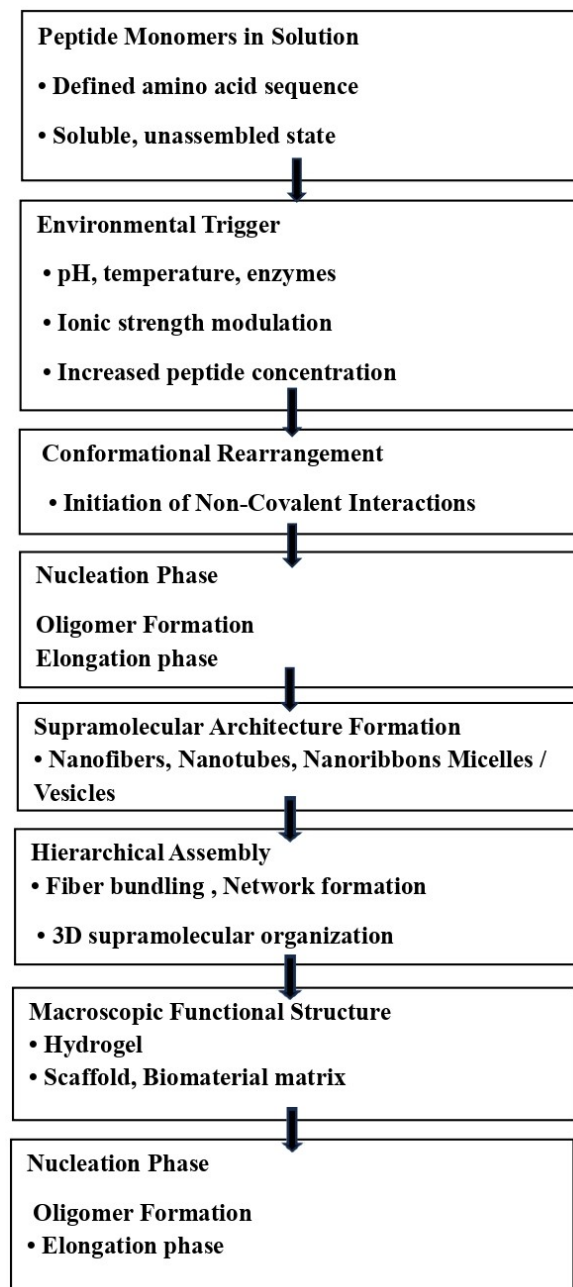


Figure 1: Flow diagram depicting the mechanism of peptide self-assembly

The first stage in designing functional peptide assemblies typically entails morphological control; in fact, it's critical to understand the nature of peptide folding, which drives self-assembly and produces a variety of unique structures. Building block types can be used to create synthetic SAPs with unique properties, primarily used in the biological field. The building blocks are meant to be peptide monomers that can self-assemble into SAPs with various morphologies.^[9]

Di-peptides

They are considered to be one of the most fundamental building components of peptide nanotechnology. Aromatic interactions among dipeptides help in the formation of tubular structures.^[10]

Surfactant-like peptides

They reduce the surface tension of water and have the unique property of being soluble in both organic solvents and water. This property is due to its amphiphilic nature, which features a hydrophobic tail and a hydrophilic head.^[9] Vauthey *et al.* suggested that surfactant-like peptides self-assemble into nanovesicles and nanotube-like nanostructures.^[9]

Peptide amphiphiles having an alkyl group

Many SAPs have a basic structure that is made of a tail that is hydrophobic and a head that is hydrophilic. This particular series of peptides is associated with hydrophobic alkyl chains. When this alkyl chain connected with a peptide block comes in contact with aqueous solutions, the tail of the peptide (hydrophobic) organizes into a 3D structure, like protein folding. Peptides typically form various structures, such as nanofibers, micelles, vesicles, nanotapes, and nanotubes.^[4]

Bolaamphiphilic peptides

Bolaamphiphiles differ from surfactant-like peptides as bolaamphiphiles have two heads that are hydrophilic in nature, joined by a hydrophobic tail, whereas surfactant-like peptides have only one hydrophilic head. As a result, the two-headed design of bolaamphiphiles has certain unique properties. Bolaamphiphiles are considered promising nanomaterials that can self-assemble into useful nanostructures.^[11]

Ionic complementary

SAPs- The unique feature of these peptides is the configuration of negatively and positively charged residues in an alternate fashion. These peptides are classified into four types based on their charge distribution, that is

a) Type 1 +-

b) Type 2, ++--

c) Type 3, +++---

d) Type 4, ++++----

This arrangement of charged amino acids is referred to as a molecular Lego.^[7]

Cyclic peptides, in terms of conformational stability, are better than linear peptides. Cyclic peptides are formed by stacking the amino acids into a cylindrical structure. Between the two amino acids is an intermolecular hydrogen bond, forming a β -sheet tubular structure. In this way, on the outside of the cylinder, we have an amino acid side chain, and on the inside, the peptide backbone. Selecting the appropriate amino acid on the side chain and the number of amino acids used in the synthesis of the cyclic peptide allows control over the external surface properties and the inner diameter.^[9]

Mechanism of self-assembling peptides in biomineralization

SAPs function through a biomimetic mechanism in which short peptide sequences spontaneously organize into three-dimensional fibrillar scaffolds in response to environmental triggers, such as acidic pH (<7) and changes in ionic strength.^[12,13] This assembly is driven by the formation of β -sheet secondary structures, which facilitate molecular alignment and hierarchical assembly into nanofibers and hydrogels.^[14]

Once formed, the 3D peptide network acts as a calcium-chelating template, binding Ca^{2+} and PO_4^{3-} ions from the surrounding medium and directing de novo nucleation and precipitation of hydroxyapatite (HAP) within its matrix.^[15,16] Even relatively simple peptide sequences containing molecular recognition motifs can organize into complex supramolecular structures, while short biomimetic sequences resembling natural proteins enhance ordered mineral crystal growth and tissue-like remineralization.^[16,17]

This mechanism has been successfully translated to clinical dentistry. Several randomized clinical trials (RCTs) have demonstrated that SAPs, particularly P11-4, can prevent and remineralize early enamel lesions, including white spot formation around orthodontic brackets, as shown by Jablonski-Momeni *et al.*^[18] Other trials further confirmed its efficacy in reducing caries activity^[19] with enhanced outcomes when combined with fluoride therapy.^[20] A recent systematic review and meta-analysis of six clinical trials further concluded that P11-4 supports caries arrest and reduction in lesion size, indicating clinically relevant remineralization capability^[21] [Table 1]. Represents summary of commonly used self-assembling peptides in dentistry, including their assembly mechanisms and current clinical status.

Applications of self-assembling peptides in dentistry

Table 1: Summary of commonly used self-assembling peptides in dentistry, including their assembly mechanisms and current clinical status.

Peptide	Assembly type	Dental application	Clinical status	Supporting references
P11-4 (SAP P11-4)	β -sheet nanofiber hydrogel	Enamel remineralization, early caries management	Clinically available; RCT-supported	[1,3,18,21,24,40]
RADA16-I	Ionic-complementary β -sheet nanofiber hydrogel	Pulp tissue engineering, bone regeneration (experimental dental relevance)	Preclinical	[37,41]
Amelogenin-derived peptides	Self-assembled nanospheres / hierarchical aggregates	Enamel biomimetic remineralization	Experimental	[13,22]
Oligopeptide amphiphiles	Amphiphilic β -sheet nanofibers	Enamel-like mineral formation	Preclinical	[29,30]
Calcium-responsive β -sheet peptides	Ion-triggered β -sheet assembly	Dentin intrafibrillar mineralization	Experimental	[12]

RCT: Randomized clinical trials, SAP: Self-assembling peptide.

Enamel remineralization

There is a growing need for new therapeutic strategies, and one promising direction involves biomimetic approaches that imitate natural biological processes. These biomimetic methods mainly fall into two groups: Amelogenin-based systems, which use natural enamel proteins or their modified forms to guide mineral formation, and rationally designed peptide systems, such as SAPs, that are synthetically created and optimized to promote remineralization and tissue repair.^[22,23] Peptide P11-4 (also known as Oligopeptide-104) is composed of five key amino acids — arginine, tryptophan, phenylalanine, glutamine, and glutamic acid. Owing to its specific sequence and charge distribution, this peptide can assemble into hierarchical nanofibrous scaffolds under appropriate environmental conditions. When P11-4 diffuses into an early carious lesion, the acidic pH (typically < 7.4) and presence of cations act as triggers, inducing the peptides to align and form β -sheet nanostructures that organize into a 3D matrix. This newly formed scaffold mimics the natural extracellular matrix and provides a template for calcium and phosphate ion deposition, thereby promoting biomimetic remineralization within the lesion.^[24] P11-4 is a brush-on liquid formulation containing a SAP that is applied after minimal chemical preparation and rinsing. The peptide, commercially known as Curodont Repair (CR), is supplied as a lyophilized powder that is rehydrated prior to application. Once in contact with the lesion environment, P11-4 self-assembles and acts as a scaffold to guide and stimulate enamel regeneration.^[21] Post-orthodontic treatment white spot lesions remain a common clinical concern, and evidence indicates that SAP exhibits superior remineralization potential compared to fluoride^[25] while demonstrating no adverse effect on bracket shear bond strength, thereby supporting their use as a preventive application prior

to orthodontic bonding.^[26] Broseler *et al.* (2020), in a randomized controlled trial, reported that early carious lesions treated with P11-4 showed a significantly greater reduction in size compared to those treated with fluoride varnish.

Rationale behind use of p 11-4

Fluoride has long been recognized as one of the most effective agents for caries prevention due to its well-established cariostatic and remineralizing properties. However, despite its ability to inhibit lesion progression, fluoride alone cannot fully eliminate caries, nor does it consistently promote deep, subsurface mineral penetration within advanced lesions. This limitation has encouraged the exploration of regenerative approaches that aim not only to arrest caries but also to restore lost mineral content within enamel, a concept now referred to as guided enamel remineralization (GER).^[24]

According to a recent comprehensive review and meta-analysis, CR likely has clinically significant effects on reducing lesion size and arresting caries.^[21] Fluoride and the SAP P11-4 work better together, probably because of their complementary mechanisms and sites of action. While P11-4 penetrates the sub-surface body and forms a three-dimensional matrix that subsequently becomes mineralized by inducing de novo hydroxyapatite nucleation, fluoride is primarily integrated in the intact surface of the initial carious lesion, with little entering the subsurface lesion body.^[1]

Many studies have concluded that fluoride application combined with P11-4-facilitated biomimetic mineralization provides a straightforward, safe, and efficient non-invasive treatment for early carious lesions, superior to the currently accepted gold standard of fluoride alone. This innovative method has the potential to shift clinical dentistry from

a restorative to a therapeutic approach by regenerating enamel tissue and stopping lesion development. Preventing further loss of healthy hard tissue during invasive restorative procedures can prolong the tooth's life and reduce long-term medical expenses.^[3]

The influence of fluoride percentage and treatment duration should be interpreted considering the distinct but complementary mechanisms of P11-4 and fluoride. The self-assembling peptide P11-4 promotes biomimetic remineralization by forming a three-dimensional scaffold within early enamel lesions, facilitating guided mineral deposition in the subsurface region.^[3,24] In contrast, fluoride enhances remineralization primarily by promoting fluorapatite formation and improving enamel resistance to demineralization.^[23,34] Clinical evidence demonstrates that the adjunctive use of fluoride with P11-4 results in significantly greater lesion regression compared with fluoride alone, indicating a beneficial combined effect when used within appropriate clinical protocols.^[1,20,21] Therefore, differences in fluoride concentration across studies may contribute to variations in remineralization outcomes, particularly when comparing monotherapy with combination approaches.

Treatment duration is also a critical determinant of efficacy. Both in situ and randomized clinical trials have shown that the remineralizing effect of P11-4 progresses over time, with greater lesion regression observed during extended follow-up periods.^[1,18] Furthermore, systematic evaluations confirm that improvements in caries arrest and lesion regression become more evident with continued monitoring.^[21,24] Consequently, discrepancies in follow-up duration among studies may partially explain differences in reported outcomes between P11-4 alone and P11-4 combined with fluoride.

Dentin remineralization

With advancements in tissue engineering, novel biomimetic strategies have been introduced, leading to the development of delivery systems capable of remineralization and antibacterial action. Among these, SAPs have gained particular attention as a promising approach for dentin biomineralization. SAPs possess the ability to organize into three-dimensional fibrillar networks under specific conditions—most notably at pH levels below 7 and in environments with altered ionic concentration—primarily due to their inherent β -sheet secondary structure.

Once assembled, these peptide matrices act as calcium-chelating templates that guide and initiate *de novo* hierarchical nucleation and growth of HAP. Effective dentin remineralization via SAPs relies on two key features: (1) their capacity to interact with the collagen framework through amino and carboxyl functional groups (NH_2^- , COOH^-)

commonly present in amino acids such as lysine, arginine, and glutamate; and (2) the presence of carboxylate (COO^-) domains capable of attracting calcium ions from the external environment, facilitating nucleation and mineral deposition within the demineralized matrix.

These biochemical interactions enable mineral infiltration into collagenous substrates, thereby promoting dentin repair. Moreover, SAPs have already demonstrated the safe and effective remineralization of subsurface enamel lesions by facilitating the re-formation of hydroxyapatite, further supporting their clinical relevance as biomimetic remineralizing agents.^[14]

To mimic this role, biomimetic peptides—particularly SAPs—have been developed. Through β -sheet-driven fibrillar scaffold formation, SAPs act as calcium-chelating templates that promote ACP infiltration and ordered HAP nucleation within demineralized collagen, thereby supporting intrafibrillar remineralization and restoration of mechanical properties.

Mechanistic differences between enamel and dentin remineralization

Unlike enamel, which undergoes surface-level hydroxyapatite (HAP) crystal growth, dentin remineralization is collagen-mediated and structurally more complex. Dentin contains a collagen matrix, regulated by non-collagenous proteins (NCPs), that controls hierarchical HAP nucleation. True functional recovery depends on intrafibrillar mineralization within collagen gap zones rather than extrafibrillar deposition.

This process involves stabilization of amorphous calcium phosphate (ACP) nanoprecursors that infiltrate collagen fibrils and transform into apatite crystallites. As collagen alone has limited nucleating ability, NCPs are essential for ACP stabilization and controlled mineralization.^[14]

Hypersensitivity of dentine

It is defined as a “Transient and sharp pain or discomfort in response to external stimuli such as temperature, chemicals, osmotic pressure, and mechanical effects”. The phenomenon is explained by hydrodynamic theory. The treatment used can be broadly classified into two mechanisms: stabilizing the exposed nerve endings and altering fluid flow.^[26]

To stabilize nerve endings, potassium salts are typically used, which reduce excitability by increasing potassium concentration. However, the efficacy of potassium salts remains debated. To alter fluid flow, functional compounds that can precipitate in the tubules and either block them or facilitate new mineral formation are considered for use.

The main inorganic component of the tooth is HAP. The formation and growth of which is controlled and regulated by non-collagenous proteins (NCP) like amelogenin for enamel and dentine phosphoprotein for dentine.^[26] Cementum protein 1 (CEMP1) is only expressed in cementum, and it regulates the formation of HAP in cementum.^[27]

Naturally occurring NCPs are anionic and can thereby attract calcium and initiate template biomineralization. Therefore, biomineralization has the potential to form a mineralized layer on the exposed dentine or within the dentinal tubules, protecting the pulpal nerve endings from external stimuli.^[28] Biomimetic oligopeptides composed of a repetitive amino acid sequence can partially mimic NCP and contribute to the formation of HAP. Therefore, an amphiphilic peptide that simulates CEMP1 is used to regenerate hard tissue.^[29] Oligopeptides self-assembled into a nano-matrix and function as a template for the formation of mineral precursor within 24h. However, the oligopeptide nanomatrix forms a firm bond with demineralized dentin and further resists water rinsing. This bound nano-matrix acts as a template to start the process of nucleation and transformation of HAP crystals on the demineralized dentin. After 96 hours, the oligopeptide nano-matrix forms an enamel-like tissue approximately 15.35 μm in thickness, and these regenerated enamel crystals occlude dentin tubules to a depth of 31.27 μm . Additionally, the oligopeptide nano-matrix is biocompatible with periodontal ligament cells.^[30]

Hence, “biomimetic oligopeptide simulating CEMP1 effectively induced remineralization and reconstructed hard tissues on demineralized dentin, providing a potential biomaterial for DH treatment.”^[30]

A clinical investigation was conducted to evaluate the efficacy of 8% arginine and calcium carbonate [ACC] toothpaste (control) versus the self-assembling peptide matrix (SAPM) gel (test) in the management of dentinal hypersensitivity. According to the patient questionnaire, the self-assembling peptide was associated with better levels of patient satisfaction at the earlier time points in the trial. The study concluded that both ACC and self-assembling peptides considerably reduce dentinal hypersensitivity by promoting mineral deposition at the entrances of dentinal tubules, effectively occluding them.

Erosion of enamel

Dental erosion has become increasingly prevalent due to the rise in consumption of acidic and carbonated beverages, which contain erosive agents such as citric and malic acids. These acids initiate demineralization of dental hard tissues by dissolving the inorganic component, leading to reduced surface hardness. The earliest clinical sign of enamel erosion

is a smooth, glossy appearance, which may progress to enamel loss with shallow concavities and cuspal rounding.

To counteract erosion, several strategies, including fluorides, CPP-ACP, and resin-based materials, have been explored; however, conventional fluoride toothpastes show limited efficacy against erosive challenges. Modern formulations have therefore incorporated novel biomimetic agents such as self-assembling peptide P11-4. P11-4, particularly when combined with fluoride and calcium phosphate, has demonstrated the ability to enhance remineralization and inhibit demineralization. Upon application, the peptide diffuses into subsurface microporosities and assembles into a fibrous scaffold that promotes the growth of HAP crystals for up to three months.

At low pH, P11-4 forms fibrils with negatively charged surfaces that are capable of attracting calcium ions, thereby increasing local ion concentration and potentially shifting the demineralization–remineralization balance toward mineral gain. Although the exact mechanisms require further validation, *in vitro* studies suggest that P11-4 and enamel matrix derivatives offer a protective effect against acid erosion and support the remineralization of erosive lesions.^[31]

Adhesion and whitening effect of p 11-4 on enamel

Most tooth whitening procedures use hydrogen peroxide and carbamide peroxide. These agents undergo a chemical reaction that alters tooth color.^[32]

However, these agents have side effects, including cervical root resorption and increased sensitivity. Therefore, newer agents are being developed to overcome the above problems.^[33] Recently, HAP has been proposed as a teeth whitening agent. HAP is a major constituent of teeth and can be artificially produced.^[34] HAP can be used for whitening teeth because it is a white biomaterial that adheres to teeth. The newly formed HAP layer will reflect light, making the tooth appear whiter and brighter. However, efficacy depends entirely on the level of adhesion to the tooth.^[35]

At low concentrations, the peptide-HAP solution did not differ significantly from commonly used bleaching agents. However, at higher concentrations, SEM examinations revealed the freshly synthesized peptide and HAP on the enamel surface. The study concluded that the peptide-HAP suspension is a mild tooth whitener and that peptide-HAP adhesion to enamel is concentration-dependent.^[35]

Common bleaching treatments recommend periodic applications to achieve effective results, whereas most at-home bleaching techniques require multiple applications. In contrast, peptide-HAP suspension is not dependent on the frequency of application. This is explained by the fact that the first contact of the tooth with the suspension results in an

adhesive layer of HAP particles that fully covers the enamel surface, inhibiting further chemical whitening effects from subsequent exposures. As a result, more frequent applications produced barely noticeable color variations. However, these impacts have yet to be explored *in vivo*.^[36]

Although P11-4 has demonstrated promising clinical efficacy in the management of early enamel caries, direct *in vivo* evidence supporting its role in enamel whitening and erosion prevention remains limited. Most available data in these domains are derived from *in vitro* or *in situ* models, thereby necessitating cautious clinical extrapolation and further well-designed human trials.

While several laboratory-based studies have demonstrated favorable effects on enamel surface remineralization, erosion resistance, and optical properties, these studies are conducted under controlled experimental conditions that do not replicate the dynamic oral environment. Factors such as salivary flow, pH fluctuations, dietary habits, biofilm interactions, and patient compliance may significantly influence clinical outcomes. Therefore, direct extrapolation of *in vitro* results to routine clinical practice should be undertaken with caution, and further well-designed, longitudinal *in vivo* studies are required to validate long-term effectiveness and durability.

Bone regeneration

Many SAPs are being investigated to determine their potential as scaffolds in regenerative medicine. The property of self-assembling peptides to self-assemble in response to environmental triggers, along with their ability to modify various properties such as cell adhesion, mechanical stiffness, and biodegradation, makes them an interesting material for tissue repair and regeneration.^[37]

Studies have shown accelerated healing of calvarial defects, as evidenced by cumulative total bone volume and bone mineral density values, Van Gieson histological staining, and osteocalcin and collagen type I immunostaining. This repair was not enhanced by the addition of Human Dentin Pulp Stem Cells. Mechanistic factors (including those dictating the micro-environment within the hydrogels) influencing bone repair associated with SAPs remain to be elucidated, as, indeed, does the fate of.^[38]

A self-assembling group of oligopeptides, which belong to a generation of hydrogels that form ionic self-complementary β -sheets, are the RADA16 peptides consisting of periodic repeats of the RADA sequence, where positively charged arginine and negatively charged aspartic acid alternate with each other, resulting in the formation of the peptide Ac-RADARADARADARADA-NH₂ (RADA16-I).^[39,40] Yang *et al.* (2023) reported that RADA16 enabled sustained release of growth factors from CGFs, enhancing their osteoinductive potential.^[41] They suggested that the biocompatible RADA16

nanofiber scaffold hydrogel combined with CGFs may serve as a promising therapeutic approach for alveolar bone loss and other conditions requiring bone regeneration.^[41]

At neutral pH, RADA16-I organizes into fibres, resulting in a 3D hydrogel. Compared to standard biompeptides, RADA16-I is injectable; has excellent biocompatibility and minimal cytotoxicity; and has the capacity to produce an actual 3D fibrous framework for cell development and (4) capacity to be further changed by different amino acid segments to achieve superior biological features, such as PRG, a functional segment that may increase cell adhesion and proliferation. As a result, RADA16-I offers considerable potential for 3D cell culture and tissue engineering.^[38] [Table 2] represents a summary of key clinical studies evaluating self-assembling peptides in dentistry, including study design, sample size, intervention protocol, and clinical outcomes.

Challenges of self-assembling peptides

Despite their promising regenerative and remineralization potential, SAPs face several challenges that currently limit their widespread clinical translation. The self-assembly process is highly sensitive to environmental conditions, including pH, temperature, ionic strength, and the presence of biomolecules, leading to variability in nanofiber morphology and mechanical properties. This sensitivity often leads to inconsistent assembly outcomes, which in turn affect reproducibility and scalability during manufacturing. In some cases, peptide aggregation can yield heterogeneous, poorly defined structures, making standardization difficult.

Another major hurdle lies in predicting peptide sequence behavior, as minor sequence modifications can markedly influence assembly kinetics and stability.^[42] Therefore, rational peptide design remains a complex process. Future advancements are likely to emerge from integrating computational modeling and machine-learning-based predictions with experimental validation, enabling faster discovery of optimized peptide motifs with controllable self-assembly characteristics. Additionally, *in situ* characterization tools such as cryo-electron microscopy and advanced spectroscopic techniques are essential for elucidating assembly pathways and improving design accuracy.

Despite their promising biomimetic potential, several practical considerations may limit the widespread clinical SAPs. The synthesis and large-scale production of peptide-based materials can be costly, potentially affecting affordability and accessibility. Additionally, regulatory approval pathways for peptide-based biomaterials require rigorous biocompatibility, toxicity, and long-term clinical performance data, which may delay translation into routine practice. Long-term stability within the oral environment also remains a concern, as exposure to saliva, enzymatic degradation, and

Table 2: Summary of key clinical studies evaluating self-assembling peptides in dentistry, including study design, sample size, intervention protocol, and clinical outcomes.

Author	Study design	Sample size	Intervention	Comparison	Key clinical outcomes
Alkilzy <i>et al.</i> ^[11]	Randomized controlled trial	70 patients (n=35)	P11-4 + fluoride	Fluoride alone	Significant regression of early enamel caries lesions; enhanced remineralization compared to fluoride alone
Fernández-Romero <i>et al.</i> ^[14]	Systematic review	Multiple studies	Self-assembling peptides	Various controls	Concluded SAPs show promising remineralizing potential in dentinal lesions; heterogeneity noted
Jablonski-Momeni <i>et al.</i> ^[18]	Randomized In Situ Clinical Trial	157 specimens (in situ model)	P11-4 matrix	Control	SAPM showed the prevention of caries and remineralization of enamel around orthodontic brackets
Atteya <i>et al.</i> ^[19]	Randomized Controlled Clinical Trial	66 patients	P11-4 + nano-silver fluoride (NSF)	NaF	The findings of this study highlight the remineralizing effect of P11-4 and NSF. After one year, there were no significant differences in the reduction of ICDAS scores among groups in adjusted analysis, although P11-4 and NSF showed less caries activity and lower Diagnodent scores than the NaF group.
Keeper <i>et al.</i> ^[21]	Systematic review and meta-analysis	6 clinical trials	P11-4	Various comparators	This systematic review and meta-analysis provide evidence that P11-4 is likely effective for arresting initial (noncavitated) caries lesions across 4 studies and for reducing lesion size across 2 studies.
Dawasaz <i>et al.</i> ^[24]	Comprehensive review	Multiple studies	P11-4 in dental hard tissues	Various	Concluded SAPs are effective in early enamel lesions; more long-term trials are required
Welk <i>et al.</i> ^[25]	Clinical study (Orthodontic patients)	23 patients	P11-4	Control	Reduction in orthodontic treatment-induced white spot lesions
Bröseler <i>et al.</i> ^[40]	Randomized clinical trial	37 patients	P11-4	Fluoride varnish	Within the limits of this study, it was shown that the size of early carious lesions treated with P11-4 was significantly reduced; this result was superior to that of fluoride varnish treatment

SAPs: Self-assembling peptides, SAPM: Self-assembling peptide matrix, NSF: Nano silver fluoride ICDAS:International Caries Detection and Assessment System NaF: Sodium fluoride

pH fluctuations may influence peptide integrity and sustained mineralization efficacy. Furthermore, clinical success may depend on application protocols, frequency of use, and patient compliance, particularly if repeated applications are necessary to achieve optimal outcomes. Therefore, further long-term *in vivo* and clinical studies are essential to validate the durability, safety, and cost-effectiveness of SAP-based therapies.

CONCLUSION

SAPs have emerged as a promising biomimetic strategy for minimally invasive dentistry, with the potential to regenerate enamel by forming subsurface scaffolds and facilitating ion infiltration. Evidence indicates a superior remineralization potential compared to fluoride, along with the added advantage of not compromising orthodontic bracket bond

strength, supporting their applicability for the prevention and treatment of post-orthodontic white-spot lesions. Beyond enamel regeneration, SAPs have also shown encouraging effects in the management of dentinal hypersensitivity, bone regeneration, and pulp revascularization, broadening their scope within restorative and regenerative dental therapies. Collectively, the current literature highlights SAPs as a versatile material with significant potential to enhance conservative clinical practice.

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