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ORIGINAL RESEARCH

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Comparison of antibacterial and antifungal efficacy of self-assembling peptide P_{11}-4 with different remineralization agents: an *in-vitro* microbiological study

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Abstract

Background: The aim of this study is to evaluate the effect of self-assembling peptide (SAP) P_{11}-4 on the *Streptococcus mutans* American Type Culture Collection (ATCC) 10449, *Lactobacillus casei* ATCC 11578 and *Candida albicans* ATCC 60193 and to compare the antibacterial and antifungal activity with different remineralisation agents. **Methods**: This *in-vitro* microbiological study was performed with five independent groups (G1. Chlorhexidine Gel (Best Dental, Istanbul, Turkey), G2. Profluorid Varnish® (VOCO GmbH, Cuxhaven, Germany), G3. Curodont™ Protect (Credentis AG, Windisch, Switzerland), G4. Tooth Mousse™ (GC Corporation, Tokyo, Japan) and G5. MI Paste Plus (GC Corporation, Tokyo, Japan)). The antimicrobial activities of the samples were evaluated according to 24-hour time kill assay against *S. mutans*, *L. casei* and *C. albicans*. **Results**: The control, Group 1—Chlorhexidine gel, had the strongest antibacterial activity against all of the tested microorganisms. The results showed that Group 4—Tooth Mousse™ was the most effective remineralization agent with the best antimicrobial activity against *S. mutans* and *C. albicans*, followed behind respectively with Group 5—MI Paste Plus, Group 3—Curodont™ Protect, and Group 2—Profluorid Varnish®. Group 5—MI Paste Plus demonstrated the most effective antibacterial activity against *L. casei*. Group 4—Tooth Mousse™, Group 2—Profluorid Varnish®, and Group 3—Curodont™ Protect were afterwards in order. **Conclusions**: SAP P_{11}-4 can be used as an antimicrobial agent to prevent opportunistic fungal infections as well as to prevent and halt the progression of incipient lesions.

Keywords

Self-assembling peptide; Tooth remineralization; Sodium fluoride; Casein Phosphopeptide-amorphous calcium phosphate; Antibacterial; Antifungal

1. Introduction

The most prevalent non-communicable disease around the world is dental caries. People of all ages, from young children to the elderly, are affected by dental caries. The basis of caries formation is the predominance of acidogenic bacteria in the biofilm. The fermentation of carbohydrates by these bacteria and the resulting organic acids lower the pH level and cause a mineral loss in dental hard tissue. Dental caries depends on host, microorganism, diet and time factors, but many environmental factors also play an active role in its development. Regulation of environmental factors, avoidance of cariogenic diet, removal of dental plaque and good oral hygiene can be preventive applicants to dental caries [1]. To keep dental tissue from breaking down, the cycle of demineralization and remineralization must be balanced. Once the balance is disturbed and demineralization increases by mineral loss on the tooth surface, tissue loss occurs and restorative options are left for treatment. Initial enamel caries are characterized by a white chalky appearance without cavitation and are called “white spot lesions”. Early detection and treatment of the white spot lesions will be crucial in slowing down the caries progression and consequent destruction of the tooth’s structure [2, 3].

The most widely known and used remineralization agents are fluoride-based solutions, gels and varnishes. Topical fluoride applications convert hydroxyapatites on the enamel surface into fluorapatites, which are more acid-resistant. It also prevents bacteria in dental plaque from fermenting sugars and prevents the environment from becoming acidic. Oral care products containing fluoride are effective in the remineralization of enamel. However, they do not have the potential to promote the formation of organized apatite crystals [4].

Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) is an agent that is used for biomimetic

remineralization. It is composed of CPP in the milk products and ACP, which provides apatite formation. The caries preventive effect of CPP-ACP is explained by these mechanisms; when CPP-ACP is exposed to an acidic effect, ACP is released from the compound. Calcium and phosphate ions released into the environment are incorporated into the structure of the dental plaque, buffering the acidic environment of the plaque and balancing the pH level [5, 6]. Casein Phosphopeptide-Amorphous Calcium Fluoro Phosphate (CPP-ACFP) is obtained by adding fluoride to CPP-ACP. Calcium and phosphate in plaque contribute to remineralization by increasing the fluoride ion level [7].

A current and innovatively developed agent, self-assembling peptide (SAP) P_{11}-4 is being used in biomimetic remineralization and enamel regeneration. SAP P_{11}-4 is a synthetic, pH-regulated oligopeptide that stimulates the formation of *de novo* hydroxyapatite derived from saliva, mimicking the amelogenesis and enamel matrix proteins [8]. It contains natural amino acids, including glutamine, glutamic acid, phenylalanine, tryptophan and arginine. SAP P_{11}-4, a low-viscosity isotropic liquid, diffuses rapidly deep into the lesion when applied to the caries lesion [9]. Due to the increase of cations in the carious lesion, the presence of an acidic environment and high ionic strength, the peptide self-assembly system is activated. Especially when the pH level drops below 7.5, the SAP P_{11}-4 changes from an isotropic liquid to an elastomeric nematic gel. In this gel form, P_{11}-4 monomers come together in bands and ribbons with rapid self-organization. This organization process continues over the next 24 hours to form fibrils and fiber nanostructures [10–12]. SAP P_{11}-4 fibrils, which spread to the lesion site, form three-dimensional scaffolds mimicking the enamel matrix proteins present during amelogenesis. Due to their affinity for minerals, these fibrils attract Ca^{2+} ions present in saliva and play a nucleating role in hydroxyapatite formation [13].

In addition to their mineral gain effects on dental hard tissue, remineralization agents also have effects on oral microbiota and cariogenic bacteria in dental plaque. Within the microbial community residing in dental plaque, *Streptococcus mutans*, a facultative gram positive anaerobe, holds a prominent hierarchical position characterized by its exceptional acid tolerance and acidogenic properties within the acidic environment of plaque. This pivotal role significantly contributes to the advancement of carious lesions [14]. Physiological traits of *S. mutans* essential for the onset of dental caries encompass their capacity to generate extracellular polysaccharides using sucrose, promoting robust attachment to teeth and fostering tight cell grouping, swift conversion of carbohydrates into acids, and resilience against low pH environments [15, 16]. Lactobacilli spp. have also been suggested to be significant contributing species in dental caries, they are highly capable of producing acid and surviving in acidic environments, but they do not readily establish themselves on tooth enamel [17]. Instead, they are frequently found through culturing from existing carious lesions [18]. Apart from caries-causing bacteria, another microorganism frequently found in the oral microbiota is Candida spp. *Candida albicans*, a eukaryote and an opportunistic fungus, is positively relative to the severity of childhood caries and interacts with *S. mutans* [19]. *C. albicans* can attach to enamel, and the first stage of attachment is facilitated by a robust interaction between adhesins on the yeast cell wall and the salivary pellicle [20]. In addition to its association with cariogenic microorganisms, *C. albicans* is increasing in the use of removable orthodontic appliances and space maintainers [21].

Remineralization agent's impact on dental biofilm and their effects on cariogenic bacteria and fungus in oral microbiota should also be investigated. The effect of SAP P_{11}-4 on microorganisms in the oral microbiota by comparing it with different remineralization agents consists of two studies on *S. mutans* in the literature [22, 23]. This study is the first in the literature to evaluate the efficacy of SAP P_{11}-4 on Lactobacilli spp. and Candida spp. Therefore, the current investigation aimed to evaluate and compare the efficacy of different tooth remineralization agents (G1. Chlorhexidine Gel (Best Dental, Istanbul, Turkey), G2. Profluorid Varnish® (VOCO GmbH, Cuxhaven, Germany), G3. Curodont™ Protect (Credentis AG, Windisch, Switzerland), G4. Tooth Mousse™ (GC Corporation, Tokyo, Japan) and G5. MI Paste Plus (GC Corporation, Tokyo, Japan)) on *Streptococcus mutans*, *Lactobacillus casei* and *Candida albicans* counts.

2. Materials and methods

An observational *in-vitro* microbiological study was designed. The materials used in the experiment, including their ingredients, manufacturer, lot number and pH, were presented in Table 1. The pH of the materials was measured using a pH meter (HI 5521, Hanna Instruments, Woonsocket, RI, USA).

Antimicrobial activity was tested according to Gayas *et al.* [23] with a slight modification. The initial microorganism suspension concentration was adjusted to 1.5×10^8 colony-forming unit (CFU)/mL with the McFarland scale and checked by colony counting during the experiments. Therefore, the decrease in the number of microorganisms reflects the real values. *S. mutans* ATCC 10449 (American Type Culture Collection, Fiocruz, Rio de Janeiro, RJ, Brazil), *L. casei* ATCC 11578 and *C. albicans* ATCC 60193 were cultured in Mitis Salivarius agar (Difco™, Sparks, MD, USA) with 15% (w/v) sucrose (Difco™, Sparks, MD, USA), MRS Agar (Difco™, Sparks, MD, USA) and Sabouraud Dextrose Agar (Difco™, Sparks, MD, USA) respectively at 37 °C for 24 h [24, 25]. *S. mutans* ATCC 10449 and *L. casei* ATCC 11578 plates were incubated in an atmosphere containing 8% carbon dioxide (CO_2). After incubation one colony from 24-hour cultures was transferred to 5 mL liquid medium suitable for each microorganism and incubated for another 4 h at 37 °C. Counts of microorganisms in the suspensions were adjusted to 1.5×10^8 CFU/mL using McFarland 0.5 standard. 50 μL of the culture suspensions were mixed with 50 μL test materials in a sterile Eppendorf tube and mixtures were further incubated for 1 h at 37 °C at the same conditions above. 1 mL sterile broth media were added to the tubes and vortexed for 30 s. Serial dilutions were inoculated for each microorganisms to the media and incubated for 24 h at 37 °C. Colony counts were calculated and all tests were done in duplicate.

TABLE 1. Remineralization agents used in the present study.

Materials	Lot Number	Manufacturer	Ingredients	pH level
G1. Chlorhexidine gel	17110027	Best Dental, Istanbul, Turkey	Chlorhexidine gluconate gel	6.44
G2. Profluorid Varnish®	2403704	VOCO GmbH, Cuxhaven, Germany	Ethanol, sodium fluoride (NaF)	6.42
G3. Curodont™ Protect	18-1771	Credentis AG, Windisch, Switzerland	Hydrogenated Starch Hydrolysate, Aqua, Hydrated Silica, Polyethylene Glycol-8 (PEG-8), Cellulose Gum, Sodium Monofluorophosphate, Aroma, Sodium Saccharin, Citric Acid, Sodium Hydroxide, Dicalcium Phosphate, Oligopeptide-104, Calcium Glycerophosphate, Sodium Chloride, Sodium Sulfate, Limonene, Cinnamal, Cosmetic Ingredients (CI) 42090	5.53
G4. Tooth Mousse™	231019H	GC Corporation, Tokyo, Japan	Pure water, glycerol, Casein Phosphopeptide Amorphous Calcium Phosphate (CPP-ACP), D-sorbitol, Sodium Carboxymethyl Cellulose (CMC-Na), propylene glycol, silicon dioxide, titanium dioxide, xylitol, phosphoric acid, favoring, zinc oxide, sodium saccharin, ethyl. p-hydroxybenzoate, magnesiumoxide, guargum, propylp-hydroxybenzoate, butyl p-hydroxybenzoate	7.12
G5. MI Paste Plus	230918J	GC Corporation, Tokyo, Japan	Pure water, glycerol, CPP-ACP, d-sorbitol, CMC-Na, propylene glycol, silicon dioxide, titanium dioxide, xylitol, phosphoric acid, sodium fluoride, flavoring, sodium saccharin, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butyl p-hydroxybenzoate	7.09

PEG 8: Polyethylene Glycol-8; CI: Cosmetic Ingredients; CPP-ACP: Casein Phospopeptide Amorphous Calcium Phosphate; CMC-Na: Sodium Carboxymethyl Cellulose.

3. Results

Table 2 compares the mean colony-forming units (CFUs) for antibacterial and antifungal efficiency between different groups. The test results demonstrate that Group 1 showed mean 0 CFU/mL, Group 2 showed 2.8 × 10^6 CFU/mL, Group 3 showed 2.4 × 10^6 CFU/mL, Group 4 showed 2.0 × 10^6 CFU/mL, and Group 5 showed 2.2 × 10^6 CFU/mL for *S. mutans* counts. According to results Group 1 showed mean 0 CFU/mL, Group 2 showed 6.0 × 10^6 CFU/mL, Group 3 showed 7.0 × 10^6 CFU/mL, Group 4 showed 1.4 × 10^5 CFU/mL, and Group 5 showed 8.0 × 10^4 CFU/mL for *L. casei* counts. Based on the findings Group 1 showed mean 0 CFU/mL, Group 2 showed 2.8 × 10^5 CFU/mL, Group 3 showed 7.2 × 10^3 CFU/mL, Group 4 showed 2.8 × 10^3CFU/mL, and Group 5 showed 3.2 × 10^3 CFU/mL for *C. albicans* counts.

Group 1—Chlorhexidine gel tested as a control showed most antimicrobial effect on all microorganisms in the study as expected. Group 4—Tooth Mousse™ was found to be the most effective on both *S. mutans* and *C. albicans* followed respectively by Group 5—MI Paste Plus, Group 3—Curodont™ Protect and Group 2—Profluorid Varnish®. Group 5—MI Paste Plus was the most successful in the antibacterial effect on *L. casei*, respectively being followed by Group 4—Tooth Mousse™, Group 2—Profluorid Varnish® and Group 3—Curodont™ Protect.

4. Discussion

As the principal causative agent of dental caries, *S. mutans* attaches actually to the salivary pellicle of enamel and other microorganisms in the plaque community to begin the colonization process on the surface of the tooth, which eventually causes damage to the dental hard tissues [26]. A count of *S. mutans* exceeding 10^5 colony-forming units (CFUs) per millilitre of saliva serves as an indicative marker for high caries risk [27]. Lactobacilli spp., known for their pronounced acidogenic and aciduric traits, are isolated from mature carious lesions [28]. A critical concentration of 10^5 CFU/mL of saliva is required to identify Lactobacilli spp. on enamel surfaces. It is noted that while Lactobacilli spp. function a secondary colonizer, *S. mutans* acts as the primary instigator of cariogenic processes [29]. *C. albicans* is an opportunistic microorganism observed in the oral microbiome and may be involved in the caries formation through its synergistic relationship with *S. mutans* [19]. To prevent or reduce the progression of dental caries, remineralization agents are employed to promote the mineralization of the tooth surface, enhancing its resistance to acid attacks. In addition to their remineralization capacity, these agents also have effects on the number and colonization of microorganisms.

Chlorhexidine gel was used in the control group in this study and was found to be effective *on S. mutans*, *L. casei* and *C. albicans*, zeroing their counts. Chlorhexidine gel can be

TABLE 2. Antibacterial and antifungal activity of the test materials for groups.

Microorganisms	Groups								
	G1	G2 (CFU/mL)	G2 Δlog	G3 (CFU/mL)	G3 Δlog	G4 (CFU/mL)	G4 Δlog	G5 (CFU/mL)	G5 Δlog
S. mutans ATCC 10449	0	2.8×10^6	1.72	2.4×10^6	1.78	2.0×10^6	1.86	2.2×10^6	1.82
L. casei ATCC 11578	0	6.0×10^6	1.39	7.0×10^6	1.32	1.4×10^5	3.02	8.0×10^4	3.26
C. albicans ATCC 60193	0	2.8×10^5	2.72	7.2×10^3	4.31	2.8×10^3	4.72	3.2×10^3	4.66

G1: Chlorhexidine Gel; G2: Profluorid Varnish®; G3: Curodont™ Protect; G4: Tooth Mousse™; G5: MI Paste Plus; ATCC: American Type Culture Collection; CFU: colony-forming unit.

used both personal and/or professional usage. Research has shown that frequent application (3–4 times daily for 2 days or once daily for 10–14 days) may lead to a decrease in *S. mutans* levels, although there are significant differences in its effectiveness among individuals [30]. While chlorhexidine has been shown to have antibacterial properties against *S. mutans* in the mouth, there is limited evidence regarding its ability to prevent the development of dental cavities [31].

Fluoride gels (5% Sodium fluoride (NaF)) are the most commonly used remineralization agents and studies investigating their effects on microorganisms are available in the literature. In the study by Erdem *et al.* [32], effect of Bifluoride 12 (6% NaF and 6% Calcium fluoride (CaF_2); Voco, Cuxhaven, Germany) on *S. mutans* counts after 24 hours evaluated and founded that 1.3×10^6 CFU/mL and Profluorid Varnish® used in our study was 2.8×10^6 CFU/mL, which is a little bit less effective on *S. mutans*. In the same study, the effect of Fluor Protector (1% difluorsilan; Vivadent, Schaan, Liechtenstein) on *S. mutans* count was also evaluated and was found to be 3.0×10^3 (CFU/mL) [32], much more effective than the fluoride gel we used in present study.

CPP-ACP has been shown to alter the bacterial biofilm environment to one that is less pathogenic and to reduce the virulence of bacteria in recent studies that examined the impact of CPP-ACP products on bacterial counting, acidogenicity, and proportion of bacteria species linked to caries and health [33]. It was noticed that CPP-ACP and CPP-ACFP caused a greater decrease in the counts of *S. mutans* and *L. casei* more than fluoride gel and SAP P_{11}-4. In the study by Al-Haj Ali *et al.* [34] the effect of CPP-ACP and silver diamine fluoride on *S. mutans* count was evaluated. In the effect of CPP-ACP on *S. mutans* count, a value of 9.6×10^7 CFU/mL was obtained, while the value we obtained in our study was much less and was 2.0×10^6 CFU/mL.

Also, CPP-ACP and CPP-ACFP showed antifungal properties on *C. albicans* and decreased their counts to respectively 2.8×10^3 CFU/mL and 3.2×10^3 CFU/mL, and the antifungal effect was similar to that of SAP P_{11}-4 (7.2×10^3 CFU/mL) but higher than fluoride gel (2.8×10^5 CFU/mL). In the study by Monica *et al.* [35], the effect of CPP-ACP and virgin coconut oil mousse on the number of *C. albicans* was examined. A value of 2.0×10^2 CFU/mL was obtained for CPP-ACP on the number of *C. albicans*, which was much higher in our study at 2.8×10^3 CFU/mL.

Studies evaluating the antimicrobial efficacy of sodium fluoride-containing gels and remineralization agents such as CPP-ACP and CPP-ACFP are available in the literature, but there are no studies comparing SAP P_{11}-4. SAP P_{11}-4 is marketed commercially as "Curolox® Technologies", along with the "Curodont™ Repair" and "Curodont™ Protect" products. Curodont™ Protect is a polymeric SAP matrix with 1000 ppm P_{11}-4, 900 ppm fluoride, and 900 ppm calcium phosphate that is intended for use in clinics or homes. Moreover, P_{11}-4 has distinct formulations, concentrations, and two main mechanisms of action. When administered to surface carious lesions, the monomeric form diffuses into the lesion body, whereas the polymeric form functions largely on the tooth surface to preserve the tooth minerals. This occurs as a result of the polymeric form's fibres being too lengthy to diffuse into the lesion body [36]. There are only two *in-vitro* studies [22, 23] in the literature evaluating the antimicrobial efficacy of SAP P_{11}-4 (Curodont™ Protect) just on *S. mutans*. In the study by Gayas *et al.* [23], the effects of SAP P_{11}-4 (Curodont™ Protect, Switzerland), fluoride enhanced hydroxyapatite gel (Remin Pro®, Germany), acidulated phosphate fluoride gel (Insta Topical Gel, India), chlorhexidine gluconate gel (Hexigel®, India) and normal saline on *S. mutans* counts were evaluated and compared. While the Curodont™ Protect effect on *S. mutans* count was $8.41 \pm 3.51 \times 10^5$ CFU/mL in the study, the value we obtained in our study was 2.4×10^6 CFU/mL, the decrease seen in the two studies was not microbiologically excessive and the results supported each other. The effect of ReminPro® on the number of *S. mutans* is 10.03×10^6 CFU/mL, while the effect of Profluorid Varnish® we used is 2.8×10^6 CFU/mL, and the antibacterial properties of the remineralization agent we used in our study are higher [23]. Chandran *et al.* [22] compared the antimicrobial effect of Curodont™ Protect and silver diamine fluoride on *S. mutans*. They used chlorhexidine gluconate gel as a positive control and distilled water as a negative control. When the antimicrobial activity was compared using the agar well diffusion method, silver diamine fluoride created 38.33 ± 0.58 mm, chlorhexidine gluconate gel 26.67 ± 0.58 mm and Curodont™ Protect 0 mm zone of inhibition in *S. mutans* [22].

The effects of the remineralization agents used in the study on the number of *S. mutans* are similar to each other. Fluoride gel is more effective than SAP P_{11}-4 in reducing the number of *L. casei*. SAP P_{11}-4 is more effective than fluoride gel in decreasing the number of *C. albicans*. It is assumed that the slightly noticeable antimicrobial effect of SAP P_{11}-4 is due to the Arginine and Tryptophan content [37]. Arginine

and tryptophan are non-structured peptides with a wide range of antimicrobial effects. Upon interaction with a membrane, they typically reconfigure into amphipathic structures, causing leakage. Additionally, they interfere with intracellular bacterial processes by inhibiting nucleic acid synthesis, protein production, or other enzyme activities like cell-wall synthesis [38]. Furthermore, Curodont™ Protect does not only contain SAP P_{11}-4, and in fact the presence of fluoride is thought to promote antibacterial activity. Another possible explanation for the antimicrobial effect is that the application of SAP P_{11}-4 may lead to a reduction in enamel surface roughness, as indicated in earlier studies [39]. This could be significant because *S. mutans* has been found to adhere more readily to rough surfaces [40].

In all of the microbiological performed on SAP P_{11}-4 only Curodont™ Protect was used, therefore in the future, new studies are needed to that evaluate the antimicrobial properties of the remineralization agent consisting only of SAP P_{11}-4 without fluoride.

5. Conclusions

SAP P_{11}-4 shows similar antibacterial properties to fluoride gel on *S. mutans* and *L. casei*. SAP P_{11}-4 shows a superior antifungal effect on *C. albicans* compared to fluoride gel. SAP P_{11}-4 can be considered as efficacious in the prevention and interception of the progression of incipient lesions, in addition, to preventing opportunistic fungal infections.

ABBREVIATIONS

SAP, self-assembling peptide; CPP-ACP, Casein Phosphopeptide-Amorphous Calcium Phosphate; CPP-ACFP, Casein Phosphopeptide-Amorphous Calcium Fluoro Phosphate; CaF_2, Calcium Fluoride; NaF, Sodium Fluoride; ATCC, American Type Culture Collection; CFU, colony-forming unit; PEG 8, Polyethylene Glycol-8; CI, Cosmetic Ingredients; CMC-Na, Sodium Carboxymethyl Cellulose; *S. mutans*, *Streptococcus mutans*; *L. casei*, *Lactobacillus casei*; *C. albicans*, *Candida albicans*.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author, Asst. Prof. Aslı Aşık, PhD, DDS, upon reasonable request.

AUTHOR CONTRIBUTIONS

AA and DÇ—conceived the idea. DAK and AU—collected and analyzed the data. AA, DAK, DÇ and AU—led the writing and revised the manuscript and gave final approval of the version to be published and agreed to be accountable for all aspects of the study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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