IN SILICO DESIGN OF CHIMERIC PEPTIDES FOR INFECTION-RESISTANT IMPLANT COATINGS

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ABSTRACT

IN SILICO DESIGN OF CHIMERIC PEPTIDES FOR INFECTION-RESISTANT IMPLANT COATINGS

Tooth loss has been a widespread dental problem affecting patients of various ages. Replacement of lost teeth with implants is a common practice for managing tooth loss due to their mechanical properties and natural-looking aesthetics. One of the persistent problems associated with dental implants is the risk of infection (peri-implantitis) which can occur when bacteria colonize the implant surface leading to inflammation and tissue damage with an eventual implant failure. Infection-resistant antimicrobial coatings have been one of the promising solutions to combat implant infections. The purpose of this study was to design functional chimeric peptides using antimicrobial peptides and hydroxyapatite binding peptides in order to provide an antimicrobial effect to hydroxyapatite-coated titanium dental implants. For this purpose, since titanium implants coated with hydroxyapatite show long-term biocompatibility, chimeric peptides that can provide antimicrobial resistance have been designed by considering antimicrobial peptides in addition to these coatings. Computational analysis, solubility analysis, secondary structure analysis, and conformational change analysis were performed to examine the ability of these formed chimeric peptides to retain their antimicrobial properties. Promising candidates obtained from secondary structure analysis and solubility analysis were examined to preserve their structure and stability by performing conformational change analysis, and the most suitable candidates were decided. Although the results give candidates computationally according to the analysis, these candidates should be confirmed experimentally. When the results from the computational analysis are validated by the experimental analysis, it will set the standard for antimicrobial chimeric peptide design.

ÖZET

ENFEKSİYONA DİRENÇLİ İMPLANT KAPLAMALARI İÇİN IN SILICO KİMERİK PEPTİT TASARIMI

Diş kaybı, çeşitli yaşlardaki hastaları etkileyen yaygın bir problem olmuştur. Kaybedilen dişlerin implantlarla değiştirilmesi, mekanik özellikleri ve doğal görünümlü estetikleri nedeniyle diş kayıplarını telafi etmek için yaygın bir uygulamadır. Dental implantlarla ilişkili kalıcı sorunlardan biri, bakterilerin implant yüzeyini kolonize ederek enflamasyona, doku hasarına ve nihai bir implant başarısızlığına yol açtığındaki ortaya çıkabilen enfeksiyon (peri-implantitis) riskidir. Enfeksiyona dirençli antimikrobiyal kaplamalar, implant enfeksiyonlarıyla mücadelede umut verici çözümlerden biri olmuştur. Bu çalışmanın amacı, hidroksiapatit kaplı titanyum dental implantlara antimikrobiyal etki sağlamak için antimikrobiyal peptidler ve hidroksiapatit bağlayıcı peptid kullanarak fonksiyonel kimerik peptidler tasarlamaktır. Bu amaç ile, hidroksiapatit ile kaplanmış Titanyum implantlar uzun vadeli biyouyumluluk gösterdiği için bu kaplamalara ek olarak antimikrobiyal peptitler ele alınarak antimikrobiyal direnç sağlayabilecek kimerik peptitler dizayn edilmiştir. Oluşturulmuş bu kimerik peptitlerin antimikrobiyal özelliklerini koruyabildiklerini incelemek için hesaplamalı olarak ikincil yapı analizi, çözünürlük analizi ve konformasyonel değişim analizi yapılmıştır. İkincil yapı analizi ve çözünürlük analizinden elde edilen umut vadeden adayların konformasyonel değişim analizi yapılarak yapısını ve stabilitesini korumaları incelenmiş olup en uygun adaylara karar verilmiştir. Sonuçlar, yapılan analizlere göre hesaplamalı olarak adayları veriyor olsa da bu adaylar deneysel olarak konfirme edilmelidir. Hesaplamalı analiz ile elde edilecek sonuçlar deneysel analiz ile valide edildiğinde antimikrobiyal kimerik peptit dizaynı için bir standart oluşturmuş olacaktır.

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ABBREVIATIONS

TiO2	Titanium Dioxide
PPI	Proton Pump Inhibitor
PRP	Platelet Rich Plasma
ADSCs	Adipose-derived Stem Cells
PEG	Poly Ethylene Glycol
AMPs	Antimicrobial Peptides
CMC	Critical Micelle Concentration
GEPI	Genetically Engineered Peptides for Inorganics
SAMs	Self-assembled Monolayers
MIC	Minimum Inhibitory Concentration
SOPMA	Self-optimized Prediction Method
SSCP	Secondary Structural Content Prediction
SLB	Support Lipid Bilayer
MD	Molecular Dynamics

CHAPTER 1

INTRODUCTION

1.1. Tooth Loss and Replacement Therapies

Tooth loss has been a significant problem in the past and the present (Saintrain and de Souza 2012). There are numerous causes of tooth loss, including profound dental decay, periodontal disease, vertical fractures, and traumas (Rousseau et al. 2014; Thakur, Guleria, and Bansal 2016; Amadori et al. 2017; Michaud et al. 2017). All of these causes appear to be related to dietary behaviors, addictions, diseases, and accidents, among others (Brunner, Krastl, and Filippi 2009; Braly and Maxwell 1981; Mestaghanmi et al. 2018; Muhammad Ashraf Nazir n.d.). If tooth loss occurs due to these causes, numerous replacement therapies are available, including bridges, prostheses, and dental implants (Höland et al. 2009; Campbell et al. 2017; Guillaume 2016).

These replacement therapies come with some shortcomings such as surgery requirement, risk of failure, high risk of breakage, long time to heal, increased risk of gum disease, and requirement sound dental tissue (Ibbetson, Hemmings, and Harris 2017; Choi et al. n.d.; Gargallo-Albiol et al. 2019; Oh, Shiau, and Reynolds 2020; Naik 2009; Sculean, Gruber, and Bosshardt 2014). Due to food residues and inadequate replacement, bridge applications have increased the risk of periodontal disease (Vargas et al. 2015). Ingestion of dental prostheses may also result in Crohn's disease (Clemente et al. 2009). As with bridge applications, food residues pose hazards for dentures. Also, dentures are frangible due to excessive mechanical stress. Particularly, implants and implant-supported therapies necessitate surgery and a lengthy recovery period (B.Eswaran 2014).

Even though implants have disadvantages, they are currently the most popular treatment for tooth loss and are favored by the majority of patients. According to the American Academy of Implant Dentistry, 1 percent of the U.S. population has already

been implanted, and this ratio increases by 500,000 annually (Uppal 2015). Implants can be constructed from a variety of materials, including ceramics, metals, and their alloys (Duraccio, Federico Mussano, and Faga 2015). Titanium and titanium alloys are the preferred materials due to their equivalent mechanical resistance with teeth, high biocompatibility, and direct contact with bone tissue (Nicholson 2020). Conversely, titanium implants have certain limitations.

1.2. Implant Materials

Dental implants are made from various materials, but the most widely utilizied materials are titanium and zirconium (Figure 1.) (Duraccio, Mussano, and Faga 2015). Titanium has been utilized in dental implants for decades and is well-known for its durability and biocompatibility (Luo et al. 2020). It is known as a nontoxic metal and is capable of osseointegration with bone tissue (Guglielmotti, Olmedo, and Cabrini 2019). Titanium implants have a high success rate reported as up to 99% (Nicholson 2020). In addition, zirconium is a newer material, and success rate was reported as up to 92% (Rodriguez et al. 2018). Zirconium implants, which are biocompatible and have comparable strength to titanium, are frequently preferred due to their tooth-colored appearance, which can produce a more natural-looking result than titanium implants (Patil 2015). Furthermore, zirconium is highly resistant to corrosion, making it an ideal material for metal-sensitive patients (Chopra et al. 2022).

Both titanium and zirconium have advantages and disadvantages, and the option of implant material depends on some factors, including the patient's medical history, the implant's location, and the preferences of the dental professionals. In general, titanium implants are more prevalent and have a longer track record of success, whereas zirconium implants are a more recent option supported by an expanding body of research. Titanium and zirconium are both effective materials for dental implants, each with its own advantages. Patients should discuss the benefits and drawbacks of each material with their dentist in order to determine which material best suits their individual requirements.

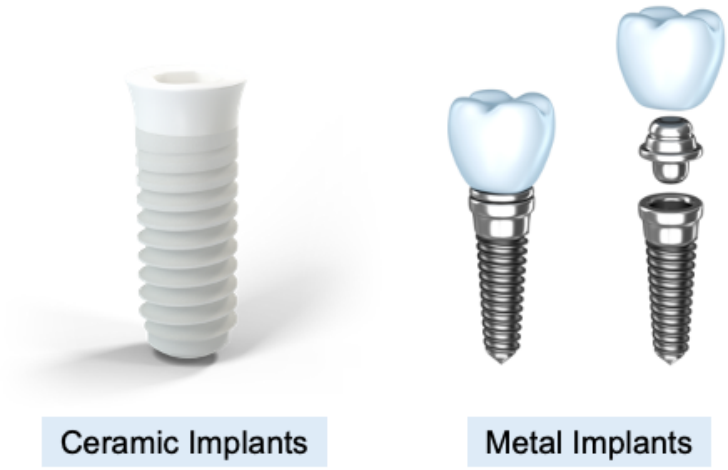

Figure 1. General Implant Materials used in Dental Implantology.

1.2.1. Titanium and Titanium Alloys

Titanium is great material for dental implants due to its low density, high strength, good corrosion resistance, and biocompatibility (Simona Baltatu et al. 2019). Titanium is significantly more compatible with bone tissue than the majority of other metals (Bosshardt, Chappuis, and Buser 2016). This characteristic is essential for the successful implantation and prolonged use of dental implants. Especially, titanium alloys are utilized specifically for high-temperature resistance or higher strength requirements, thereby enhancing the hull's properties (Dai et al. 2016). According to properties, Ti-6Al-4V is the most widely utilized metal alloy for dental implants (Åkerfeldt, Antti, and Pederson 2016).

Depending on the limitations and time period implant failure may occur (Sakka, Baroudi, and Nassani 2012; Chrcanovic et al. 2016). Early implant failure can be caused by non-sterile implants, mismatched surfaces, susceptibility to infection, smoking, and alcohol consumption (Kate, Palaskar, and Kapoor 2017; Alvim-Pereira et al. 2008; Olmedo-Gaya et al. 2016). In addition to these factors, surface oxidation and bacterial colonization may cause implant failure at a later stage (Sakka, Baroudi, and Nassani 2012).

Titanium allergy, toxicity, and infections are the primary reasons for its limitation. Titanium allergy is a late-type immune system allergic reaction, and the symptoms of titanium allergy sufferers are highly variable (Table 2). These may include basic skin lesions, contact dermatitis, muscle pain, and chronic fatigue (Goutam et al. 2014). Titanium toxicity begins with surface oxidation by dissolved oxygens in saliva; at the conclusion of surface oxidation, titanium dioxide forms on the implant surface; and if titanium dioxide particles disseminate to surrounding tissue, the patient may experience titanium toxicity. Additionally, TiO2 particles were detected in the cells of the adjacent tissue after implantation (Kim et al. 2019). Nevertheless, the success rate of titanium and alloy dental implants is exceptionally high and they have many advantages (Table 1.). According to numerous studies, implants have a success rate of up to 99 % and compared to other dental treatment methods, this rate is quite high (Karoussis et al. 2004; Nicholson 2020).

Table 1. Advantages of Titanium and Titanium Alloy Dental Implants;

Biocompatibility	Titanium and its alloys are nonreactive and compatible with body tissues. (Sidambe 2014).
Durability	Due to their exceptional strength, titanium and metal alloys are the most durable materials utilized in dental implants and are highly resistant to corrosion. (Elias et al. 2015).
Bone integration	Biocompatibility of titanium implants ensures optimal bone integration. (Guillaume 2016; Guglielmotti, Olmedo, and Cabrini 2019).
Easy sterilization	Titanium and metal alloys can be sterilized at high temperature and high pressure. Therefore, sterilization of dental implants is easy and safe (Sundaram Muthuraman 2015).
Aesthetics	The color and sheen of titanium implants are compatible with those of natural teeth. In addition, they are less visible than other implants, making them more aesthetically pleasing (Kniha et al. 2020).

Table 2. Disadvantages of Titanium and Titanium Alloy Dental Implants;

High Cost	Titanium and metal alloy dental implants are not cost-effective (Okereke, Paul Onyenegecha, and Jude Njoku 2021).
Implant-Related Infections	Titanium implants are carriers for microorganisms during the bone integration process. For this reason, the implant must be placed correctly and sterilized properly (Liaw, Delfini, and Abrahams 2015).
Risk of recurrence	There may be bone loss in some parts of the area where the implant is placed. In this case, the implant must be reinserted (Sukegawa et al. 2020).

In conclusion, titanium and titanium alloy dental implants are the most widely utilized dental implants because of their biocompatibility, durability, and bone integration properties. However, there are disadvantages, such as high costs and risk of danger. Therefore, patients who choose titanium or titanium alloys for dental implant treatment should have a thorough conversation with their specialist regarding these materials.

1.2.2. Zirconium and Zirconium Alloys

In recent years, zirconium has become a popular material for dental applications. Due to their durability, biocompatibility, and aesthetic qualities, zirconium dental implants have gained popularity (Depprich et al. 2008). Due to their lower thermal conductivity compared to titanium implants, zirconium implants may be more suitable for patients with heat or cold sensitivity (Osman and Swain 2015; Sivaraman et al. 2018).

Many studies show that zirconium dental implants have high biocompatibility, compatibility with adjacent teeth and surrounding tissues, and implant stability (Depprich et al. 2008; Michelle Grandin, Berner, and Dard 2012). According to the findings of the

research, there is a limited amount of information regarding the success rate of zirconium dental implants. Due to its outstanding biomechanical properties, biocompatibility, and tooth-like color, zirconia has been investigated as a potential substitute for titanium as a dental implant material. A research that examined the osseointegration of zirconia implants with a modified ablative surface at the ultrastructural level found that the surface characteristics of the implant affected the behavior of osteoblastic cells cultivated on the implant (Depprich et al. 2008). Another study compared bone remodeling around conventionally loaded and early-loaded titanium and titanium-zirconium alloy dental implants and found that both types of implants demonstrated excellent bone remodeling (Akça et al. 2015).

Some disadvantages of zirconium dental implants should be considered. One disadvantage is that zirconium dioxide implants generate substantially more anomalies than titanium and titanium-zirconium implants, which can negatively impact the imaging quality of cone-beam computed tomography (Sancho-Puchades, Hämmerle, and Benic 2015). The utilization of diameter-reduced implants, such as zirconium implants, may result in an over incidence of implant fractures (Gigandet et al. 2014). Moreover, commercially pure zirconium and its alloys are known for their high corrosion resistance; however, their biocompatibility is closely related to their surface properties, such as the composition of the protective oxide deposit and the surface topography (Branzoi, Iordoc, and Codescu 2008). Zirconium implants have demonstrated promise as a biocompatible, high-strength and another option to pure titanium; however, more research is required to fully comprehend their performance and potential drawbacks (Michelle Grandin, Berner, and Dard 2012).

In conclusion, zirconium and zirconium alloy dental implants offer favorable outcomes in terms of biocompatibility, esthetics, and implant stability. However, additional research is required, and titanium implants are not commonly utilized to replace them.

1.3. Dental Implant Failure

Failure of dental implants is a essential concern for both patients and dentists. According to a retrospective study, the overall implant failure rate was 10.5% over 12 years (Borba et al. 2017). Smoking, radiotherapy, diabetes, osteoporosis, bruxism, proton pump inhibitor (PPI) ingestion, implant site, and implant length are among the categories of factors that contribute to dental implant failure (H. Chen et al. 2013). Bruxism contributes to technical/biological complications of dental implants and plays a role in dental implant failure. The failure rate of prostheses in bruxers was higher than in non-bruxers, in accordance with a meta-analysis (Zhou et al. 2016). The systemic use of proton pump inhibitors (PPI) is another factor that contributes to dental implant failure. A retrospective study found that PPI intake negatively affects the osseointegration of dental implants (Ali Altay et al. 2019).

One of the factors that can affect the success or failure of dental implants is the implant site at the bone tissue (Fouda 2020). This situation reported that short dental implants are an attractive and minimally invasive alternative to bone augmentation procedures for the implantation of lengthier implants, with both groups exhibiting comparable results approximately 11 years after loading (Tallarico et al. 2020). In addition, bacterial contamination at the time of implant insertion can lead to implant failure (Deeb et al. 2015). When contemplating dental implant treatment, dentists should consider the mentioned factors. To identify additional risk factors and develop strategies to prevent dental implant failure, additional research is required.

Some common causes of dental implant failure include;

Rejection: Dental implant rejection, occurs when the body's immune system reacts negatively to a dental implant and attempts to reject it (Baseri et al. 2020).

Poor implant placement: The implant can fail if it is positioned incorrectly or if it is inserted too deeply or too shallowly (Bassir et al. 2019).

Poor bone quality: To effectively integrate with the jawbone, dental implants need a certain level of bone density. In case of the patient has inadequate bone quality, the risk of implant failure can increase (Shibli et al. 2007; Turkyilmaz and McGlumphy 2008).

Infection: Infections can occur both during and after implant implantation. In the absence of prompt treatment, an infection can result in implant failure (Deeb et al. 2015). This infection affects the tissues surrounding an implant. It is a common cause of implant failure and can occur when the patient avoids oral hygiene. (Canullo et al. 2016; Pimentel et al. 2018).

Implant fracture: Although uncommon, dental implants can fracture, particularly if the patient grinds their teeth or bites down on hard objects (Sánchez-Pérez et al. 2010).

Preventing implant failure requires detailed planning and execution of the implant implantation procedure, as well as appropriate aftercare and maintenance. To ensure the implant is in excellent condition, patients must adhere to their dentist's oral hygiene instructions, abstain from smoking, and attend regular checkups. In conclusion, dental implant failure can be due to a variety of factors, however, it can be avoided with proper planning, execution, and maintenance. Patients must collaborate closely with their dentist to ensure the long-term success of their dental implants.

1.3.1 Osseointegration

Osseointegration is the process of a direct connection between the surface of an implant and the biological bone tissue (Chang, Lang, and Giannobile 2010). For the best osseointegration process, the bone must be robust and vascular. The implant's screw thread is gently placed into the alveolar bone under anesthesia, concealed beneath the gingival mucosa, and left undisturbed for two to four months (Quiney, Brimblet, and Hodge 1990). Several implant design factors influence the osseointegration phenomenon (Coelho et al. 2015). The effectiveness of an implant depends on its biological integration, which can be severely compromised by foreign body reactions (Kaur et al. 2010). After the sterilization of surface contaminants such as bacterial debris and manufacturing residues can remain on orthopedic implants and inhibit osseointegration. (Bonsignore et al. 2011). Therefore, osseointegration is indispensable for the long-term success of dental and orthopedic implants (Parithimarkalaignan and Padmanabhan 2013).

The surface characteristics of the implant, the surgical technique used to place the implant, and the patient's overall health and immune system all influence osseointegration, according to research (Salvi et al. 2015; Sayed et al. 2021). As they provide a better environment for bone cell attachment and growth, implants with uneven or textured surfaces tend to facilitate greater osseointegration than smooth implants (Wong et al. 1995; Łukaszewska-Kuska et al. 2019). The initial stability of the implant is also essential for osseointegration, as implant micromovements can impede bone growth and integration (Salvi et al. 2015). The use of specialized surgical techniques and instruments, such as implant drills and osteotomes, can aid in the placement and stability of dental implants (Sayed et al. 2021). Several implant materials and designs have been created as a result of osseointegration research, which promotes enhanced bone growth and integration. For instance, it has been demonstrated that titanium implants with uneven surfaces have exceptional osseointegration properties and are commonly utilized in dental and orthopedic surgery (Ma et al. 2017). Other surface treatments, including hydroxyapatite coating, have also been examined for their potential to enhance osseointegration (Hermida et al. 2010). Overall, Understanding the influencing factors of osseointegration is crucial for implant placement success and long-term stability.

So, for the long-term efficacy of dental and orthopedic implants, osseointegration is a crucial procedure. The osseointegration process can be affected by implant surface characteristics, surgical technique, and patient health, according to research. Numerous researches in this area have led to the development of implant materials and designs that are more effective.

1.3.1.1 Prerequisites for Osseointegration

Osseointegration requires specific conditions for implant integration to be successful (Reyes et al. 2007). These requirements include implant design and material selection, bone quantity and quality, surgical technique, and a favorable recuperating environment.

Implant Design and Material Selection: The implant material should be biocompatible and resistant to corrosion, damage, and fracture. Additionally, the implant surface should be designed to encourage bone growth and attachment (Klokkevold et al. 1997; Oliveira et al. 2015). It is believed that roughened implant surfaces promote osseointegration (Scarano et al. 2003). Utilizing highly biocompatible implant materials, such as titanium, has produced implant systems with long-term stability (Khang et al. 2001). The geometry of an implant's surface can play a significant role in its early stabilization, thereby enhancing the dynamics of tissue regeneration (Simmons, Valiquette, and Pilliar 1999).

Bone Quantity and Quality: For the successful osseointegration of dental implants, adequate bone quantity and quality are required (Rues et al. 2021). The implant must be positioned in a region with sufficient bone volume and density to provide a stable and long-lasting interface. Important as well is the condition of the bone tissue, as poor bone quality can reduce implant stability and increase the risk of implant failure (Javed et al. 2011; Rues et al. 2021). The quantity and quality of bone are crucial to the efficacy of dental implant surgery (Şençimen et al. 2011).

Surgical Technique: Osseointegration relies heavily on the surgical technique used to implant the prosthesis. The implant must be positioned with precision and minimal damage to the neighboring bone tissue (Von Arx et al. 2013). Utilizing specialized surgical instruments, such as implant drills and osteotomes, can aid in ensuring the placement and stability of implants (Nkenke et al. 2002; Büchter et al. 2005; Bilhan et al. 2010). Bone augmentation with novel grafting materials can also promote osseointegration (Norton et al. 2003).

Healing Environment: A favorable healing environment is essential for osseointegration to be successful. Cigarette smoking, uncontrolled diabetes, and other systemic conditions that impede wound healing may impact the healing environment. In addition, good oral hygiene is necessary to prevent bacterial colonization around the implant, which can result in inflammation and bone loss (De Molon et al. 2013; Bonsignore et al. 2013).

In conclusion, successful osseointegration requires proper implant design and material selection, sufficient bone quantity and quality, an appropriate surgical technique, and a favorable healing environment. Optimal implant success requires an evaluation of the patient's bone quality and quantity, as well as their medical history and lifestyle routines.

1.3.2 Implant Infection

Dental implant infections are a prevalent cause of implant failure. *Fusobacterium spp, Streptococcus mutans, Staphylococcus epidermidis,* and *Porphyromonas gingivalis* are the bacteria most frequently associated with dental implant infections. Peri-implantitis, a type of dental implant infection, can limit clinical efficacy and impose substantial health and financial consequences on patients and healthcare providers. (Norowski and Bumgardner 2009).

Multiple factors may rise the risk of bacterial infection in dental implants. A number of factors, including poor dental hygiene, smoking, systemic diseases such as diabetes, and compromised immune systems, increase the risk of infection (Almehmadi 2019). There is a complex connection between titanium dental implants, bone, and the immune system. So, in the immune system, macrophages play a crucial role in the osseointegration process (Amengual-Peñafiel et al. 2021). The incidence of inflammatory complications following the surgical phase of dental implant placement ranges between 0.4% and 5%, and both early and late complications are possible (Tymofieiev et al. 2022). Moreover, poor oral hygiene may increase the risk of mesh infection following hernia surgery (East et al. 2022).

Using contaminated surgical apparatus or implant components during implant implantation may increase the risk of bacterial infection (Deeb et al. 2015). Signs of a bacterial infection in dental implants include pain, edema, redness, bleeding, and secretion from the implant site (Coli et al. 2017). Antimicrobial agents have been found to effectively decrease the occurrence of surgical wound infections in the field of oral implantology. It is recommended to administer antibiotic prophylaxis for Class 2 (clean-contaminated) surgical procedures, such as dental implant and bone grafting procedures, in order to maintain sufficient blood levels to combat bacterial contamination (Resnik and Misch 2008).

The "race for the surface" has been the subject of extensive study in the disciplines of biomaterials and implant dentistry (Wandiyanto et al. 2019). It refers to the competition between bacteria to colonize a surface, such as the surface of an implant, and implant manufacturers' efforts to design surface treatments that limit bacterial adhesion and enhance osseointegration (Veerachamy et al. 2014; Cox et al. 2017). Adhesion,

proliferation, and migration of biomaterials are affected by their microstructural surface topography, surface chemistry, and surface energy/wettability (Feller et al. 2015). Prior to clinical use, titanium dental implants are frequently subjected to surface modification techniques. Surface modification is a crucial stage in the fabrication of dental implants. Several techniques such as sputtering deposition, sandblasting, plasma etching, plasma spray deposition, acid etching and cathodic arc deposition, have been investigated over the years in an effort to increase the effectiveness of dental implants (Mandracci et al. 2016). Typically, porous coatings for enhanced osseointegration have a rougher surface, which makes implants more susceptible to bacterial colonization and biofilm formation (Braem et al. 2014).

The bacterial biofilm must be eliminated and a healthy peri-implant environment must be restored to treat a bacterial infection in dental implants. Non-surgical therapeutic techniques include mechanical debridement, antibacterial medications, and laser therapy. Surgical intervention, such as implantoplasty, bone grafting, or implant removal, may be necessary when non-surgical treatment fails. Good oral hygiene, routine dental examinations, and sterile surgical techniques can reduce the risk of bacterial infection during implant placement (Larsen and Fiehn 2017). The potential of silver nanoparticles to mitigate bacterial adhesion to dental implant surfaces and inhibit biofilm formation presents a promising avenue for mitigating the incidence of peri-implantitis (Sivolella et al. 2012). For the prevention of peri-implantitis, antibacterial procedures of dental implant materials have been devised, including the use of a titanium alloy containing copper and a light-curable bioadhesive hydrogel with antibacterial properties (R. Liu et al. 2016; Shirzaei Sani et al. 2019).

Patients have been advised to take prophylactic antibiotics to prevent postsurgical infections (Deeb et al. 2015). Antibiotic overuse has led to pervasive antimicrobial resistance and the emergence of multidrug-resistant bacterial strains, as supported by the results of the studies presented (Morrison and Zembower 2020; Fernández, Bert, and Nicolas-Chanoine 2016; Mancuso et al. 2021). In the field of medicine, antibiotic resistance is a growing concern for the entire human population (Perez et al., 2007). Antibiotic misuse and overuse are the primary causes of antibiotic resistance. The emergence of antimicrobial resistance is a global concern (Choudhury, Panda, and Singh 2012). The prevalence of antibiotic resistance in gram-negative bacteria has experienced a significant surge in the last twenty years. This rise has frequently been linked to elevated

rates of mortality and increased financial burdens on healthcare systems (Eichenberger and Thaden 2019).

To reduce the risk of implant failure, it is crucial to prevent bacterial infection in dental implants. Good oral hygiene, routine dental examinations, and sterile surgical techniques can reduce the risk of bacterial infection during implant placement. Overall, early recognition and treatment of bacterial infection are essential for implant preservation and the prevention of subsequent complications. As a result, various therapies are required for the prevention of infection.

1.4. Prevention Strategies for Implant Infection

Implant procedures nonetheless pose a risk of severe consequences due to implant-associated infections induced by surface-adhering bacteria that persist as biofilm (Arciola, Campoccia, and Montanaro 2018). Various strategies have been developed to prevent and treat implant infections, such as systemic and local antibiotic therapy, non-fouling surfaces, and the utilization of antimicrobial agents and peptides (Figure 2). Nonetheless, each strategy has its advantages and disadvantages. It is envisaged that the anticipated increase in the use of implanted medical devices will result in an increase in the number of infections associated with these cases.

Figure 2. Current Approaches for Developing Infection Resistant Implants.

Hence, the prevention of bacterial colonization and biofilm formation on implanted medical devices remains a significant concern. In-vivo studies have

demonstrated the efficacy of antimicrobial implant coatings in mitigating infection, inflammation, and biofilm formation (Harris et al. 2017).

1.4.1 Antibiotic Treatment

Treatment with antibiotics is a typical method for managing implant-associated infections. However, rising antibiotic resistance, the spread of antibiotic-resistant bacteria between animals and people, and the high expense of treating infections have made implant-associated infections difficult to manage (H. Li and Li 2013).

Antibiotic resistance is a major worldwide health and economic challenge. When microorganisms develop the ability to resist antibiotics, they render them useless against bacterial illnesses. Bacteria possess various mechanisms through which they can acquire resistance to antibiotics. These mechanisms encompass the inhibition of drug target accessibility, alterations in the structure and safeguarding of antibiotic targets, as well as direct modification or inactivation of medications (Blair et al. 2014). Antibiotic resistance is prevalent in both clinical and non-clinical settings. In clinical contexts, antibiotic resistance is associated with increased morbidity, prolonged hospitalization, additional expenses, and mortality (Sipahi 2014). Human activities in non-clinical situations contribute to the spread of antibiotic resistance beyond ecological boundaries, hence increasing the problem (Tripathi and Cytryn 2017).

The establishment and spread of antibiotic resistance is a worldwide issue that necessitates a diversified solution. The use of antibiotics appropriately is essential for reducing the development and spread of antibiotic resistance (Romo and Quirós 2019).

However, antibiotics are not always necessary, and their misuse and abuse contribute to the development of antibiotic resistance (Hoxha, Malaj, and Malaj 2015). In addition, the emergence of highly drug-resistant bacteria, such as carbapenem-resistant Enterobacteriaceae, highly drug-resistant Pseudomonas aeruginosa, and highly drug-resistant Acinetobacter baumannii, poses a significant threat to public health (Eichenberger and Thaden 2019). So, antibiotic resistance is a complicated and developing worldwide issue requiring a diverse solution. The use of antibiotics appropriately, as well as continuing research and development of novel medicines and

alternative therapies, are essential for reducing the emergence and spread of antibiotic resistance.

Platelet-rich plasma (PRP), which has demonstrated potential antibacterial characteristics, is an alternative strategy (H. Li and Li 2013). Also, antimicrobial coatings may be applied to implants to combat implant-related infections in patients (Vermeltfoort et al. 2008). Moreover, tethered antibiotics offer promise as a novel and feasible method for minimizing implant-associated infections (Shapiro et al. 2012).

The existing conventional susceptibility testing methods employed for microorganisms derived from infected implants do not adequately reflect the true susceptibility patterns. Consequently, the most effective antibiotic treatment approach for infections associated with implants remains undetermined. When comparing the efficacy of rifampicin-containing combinations to combinations containing vancomycin, linezolid, and daptomycin for the treatment of *Staphylococcus aureus* biofilm infections, it has been observed that the former exhibits superior results in both in vivo and in vitro settings (Jørgensen et al. 2016). In addition to the systemic administration of antibiotics, topical antibiotic prophylaxis for the prevention of surgical site infection during cardiac device installation operations has been examined (Ozyildirim 2014). Furthermore, hydrogel administration of lysostaphin has been demonstrated to eradicate Staphylococcus aureus infection of orthopedic implants and promote fracture healing (Johnson et al. 2018).

In conclusion, antibiotic therapy is a standard method for treating implant-associated infections. Due to rising antibiotic resistance and other obstacles, however, researchers have been exploring novel techniques such as platelet-rich plasma, antimicrobial coatings, and tethered antibiotics. While the ideal antibiotic regimen for treating implant-associated infections has not been determined, rifampicin-containing combinations and cefuroxime have showed good outcomes in several trials. In addition, topical antibiotic prophylaxis and hydrogel administration of lysostaphin has been explored as viable methods.

1.4.2 Antimicrobial Agents

Antimicrobial agents are crucial for avoiding implant infections, which can result in life-threatening complications or even death. Due to rising antibiotic resistance, the spread of antibiotic-resistant bacteria between animals and people, and the high cost of treating infections, implant-associated infections are posing a growing challenge to the global healthcare business. Therefore, researchers have been investigating a variety of anti-infection techniques.

Utilizing coatings that release antimicrobial agents is a technique for minimizing implant-associated infections. Researchers describe coatings that release antimicrobial agents (i.e., active release methods) for preventing implant-associated infections (Hetrick and Schoenfisch 2006). Platelet-rich plasma, which has potential antibacterial capabilities, is another method. Based on the possible antibacterial characteristics of PRP, the proposed technique that may be useful in reducing implant-associated infection (H. Li and Li 2013). Using bacteriophages as antimicrobial agents is a further innovative technique for combating implant-related infections (Moojen 2013). Despite the encouraging outcomes of several techniques, virtually none have reached the clinical application phase. Another antimicrobial agent that has been evaluated for its effectiveness in reducing implant-associated infections is sphingosine. The antibacterial effectiveness of sphingosine against sessile biofilm-grown *Staphylococcus epidermidis* was examined by researchers. The results indicated that the application of sphingosine solution resulted in the eradication of 99.9% of the microorganisms present on different implant surfaces, such as titanium, steel, and polymethylmethacrylate (Beck et al. 2020).

The effectiveness of antibiotics and antibiotic-loaded adipose-derived stem cells (ADSCs) in reducing the development of abscesses in rodents with implant-related infections has also been evaluated. In a rat model of implant-associated infection, researchers evaluated the antibacterial activity and therapeutic efficacy of antibiotic-loaded ADSCs and an antibiotic in local therapy (Yoshitani et al. 2020).

In conclusion, antimicrobial agents are crucial for avoiding implant-related infections. Numerous techniques, such as coatings that release antimicrobial chemicals, platelet-rich plasma, bacteriophages, and sphingosine that actively inhibits bacterial adherence or has intrinsic antibacterial qualities, have been investigated by researchers.

Nevertheless, several of these methods are still in the experimental phase, and further study is required to evaluate their effectiveness in avoiding implant-associated infections.

1.4.3 Nonfouling Surfaces

Non-fouling surfaces have been developed to prevent the adhesion and dissemination of microorganisms on the surfaces of implantable materials. Numerous biological applications, including diagnostic biosensors and implants that contact blood or tissue, require non-fouling surfaces (Y. Liu, Chang, and Sun 2014). The development of nonfouling surfaces is necessary for controlling the interfacial behavior of various biomedical systems, including implanted medical devices, membranes, biosensors, and devices used for storing biological fluids (Manfredini et al. 2019).

Polyethylene glycol (PEG) and its polymeric derivatives have traditionally been extensively employed as non-fouling materials in various biomedical applications such as implantation, surface modification, biosensors, and drug administration (Guo et al. 2021). Recent investigations have found zwitterionic polymers as promising alternatives to PEG-based surfaces for non-fouling properties (Ladd et al. 2008). Zwitterionic polymer surfaces consist of a homogeneous mixture of charge groups that are balanced at the nanoscale. These charge groups can be either zwitterionic or mixed charged groups. The robust hydration of these groups through ionic solvation is what allows for their stability (S. Chen and Jiang 2008). Strong surface hydration has been postulated as a primary non-fouling process contributing (Leng et al. 2015).

Super non-fouling surfaces are resistant to protein attachment and have several uses in implant technology, medication administration, blood-compatible materials, biosensors, and maritime coatings (Schmüser et al. 2016). Two strategies for preventing the adhesion and spread of bacteria on the surfaces of implantable materials are the application of antimicrobial and non-fouling coatings (Cheng et al. 2008). Biosensors, medical implants, and drug delivery vehicles rely heavily on the development of nonfouling surfaces (G. Li et al. 2010).

Several biomedical applications, including diagnostic biosensors and blood- or tissue-contacting implants, require nonfouling surfaces. The development of non-fouling

surfaces is essential for controlling the interfacial behavior of various biomedical systems, including implanted medical devices, membranes, biosensors, and devices used for storing biological fluids. Zwitterionic polymers have been identified as viable substitutes for antifouling surface materials based on polyethylene glycol (PEG). The identification of robust surface hydration has been recognized as a significant factor in the mechanisms that prevent fouling.

1.4.4 Antimicrobial Peptides

The use of antimicrobial peptides (AMPs) to prevent implant-associated infections has emerged as a viable technique. Infections of implants are a serious issue in orthopedic surgery, since they can result in implant failure, longer hospitalization, and higher healthcare expenses. AMPs are naturally occurring peptides with antimicrobial action against bacteria, viruses, and fungi. They are desirable candidates for implant coatings because they are less likely than conventional antibiotics to produce bacterial resistance.

Several studies have studied the use of AMPs in the prevention of implant-associated infections. For instance, Yazici et al. investigated the antibacterial activity of a chimeric peptide on implant material against a range of microorganisms, such as Streptococcus mutans and Staphylococcus aureus, in vitro (Hilal Yazici et al. 2016). Sjostrom et al. achieved antimicrobial Ti and Ti alloy implant surfaces by immobilizing antibiotics, AMPs, or nanoparticles to the implant surface (Sjöström, Nobbs, and Su 2016). Ishak et al. investigated the use of nature-inspired antimicrobial surfaces and AMPs to combat implant-associated infections (Ishak et al. 2022). Melicherčík et al. investigated the efficacy of short linear α-helical AMPs in treating bone infection and preventing microbial biofilm formation on model implants caused by osteomyelitis-causing microorganisms (Melicherčík, Nešuta, and Čeřovský 2018). Wisdom and colleagues conducted a study in which they designed a biomimetic interface utilizing a chimeric peptide. This peptide was created by combining a titanium binding peptide with an antimicrobial peptide (AMP) into a single molecule. The purpose of this design was to facilitate binding to the surface of an implant and provide antimicrobial properties

against two specific bacteria, namely S. mutans and S. epidermidis (Wisdom et al. 2016). Chen et al. used AMPs to functionalize titanium implants and prevent bacterial infection (J. Chen et al. 2019). Hill et al. highlighted the current role and mechanism of AMPs in preventing and eradicating orthopedic device-related infections (Hill, Jain, and Iyengar 2022).

Before an antimicrobial peptide (AMP) can be utilized as a therapeutic agent, it is necessary to fulfill several prerequisites. These include: i) demonstrating strong antibacterial activity; ii) exhibiting minimal toxicity towards mammalian membranes; iii) possessing high proteolytic stability; iv) exhibiting low serum binding; and v) being cost-effective (J. Li et al. 2017). There are numerous methods for examining AMPs, including mutation-based empirical methods, statistically-based bioinformatics methods, and MD-like tools.

AMPs work by disrupting the membranes of microbial cells. The membranes of microbial cells are made up of lipids, which are fatty molecules. AMPs are amphipathic, meaning that they have both hydrophilic (water-loving) and hydrophobic (water-hating) regions. The hydrophilic regions of AMPs interact with water, while the hydrophobic regions interact with the lipids in the microbial membrane (Moravej et al. 2018). This interaction disrupts the structure of the membrane, causing it to leak and eventually die.

Here are some of the mechanisms of action of antimicrobial peptides:

Membrane disruption: AMPs can disrupt the membranes of microbial cells, causing them to leak and die (Figure 3A) (Moravej et al. 2018; Kumar, Kizhakkedathu, and Straus 2018).

Pore formation: AMPs can form pores in the membranes of microbial cells, allowing water and ions to flow into the cells, causing them to swell and burst (Figure 3B) (Benfield and Henriques 2020; Q. Y. Zhang et al. 2021).

Protein denaturing: AMPs can denature proteins in microbial cells, making them non-functional (Figure 3C) (Kumar, Kizhakkedathu, and Straus 2018; Moravej et al. 2018).

DNA damage: AMPs can damage DNA in microbial cells, preventing them from replicating (Figure 3D) (Benfield and Henriques 2020; Q. Y. Zhang et al. 2021).

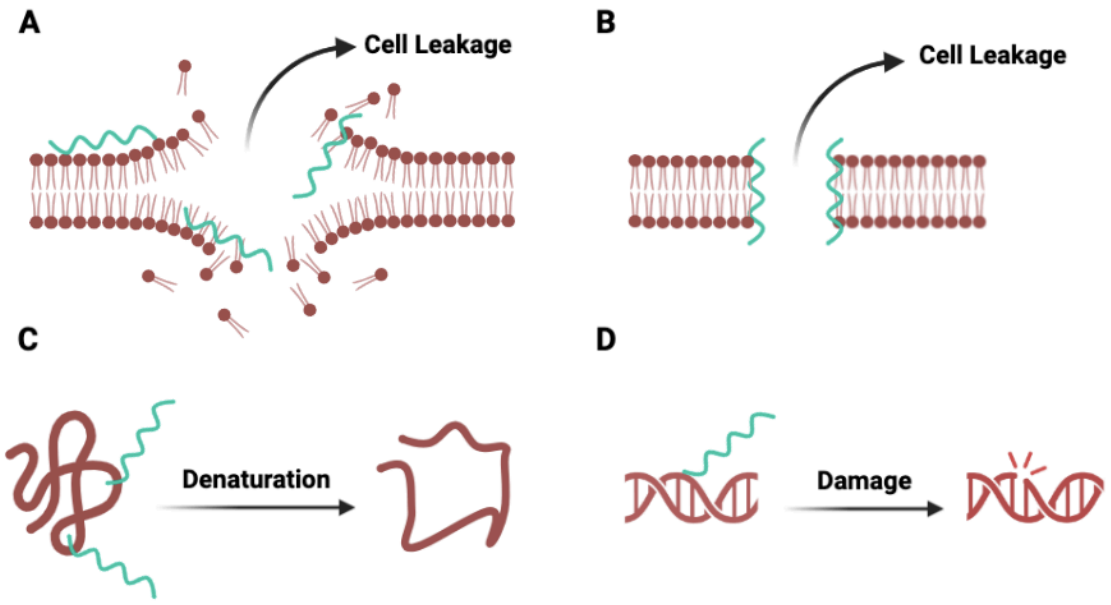

Figure 3. Mechanism of Action of Antimicrobial Peptides.

Indeed, there is a wealth of documented evidence regarding various mechanisms that lead to the instability and disruption of bacterial membranes. These mechanisms include the formation of pores or interactions with the outer leaflet. Among the extensively studied modes of action are the carpet model, toroidal pore, barrel type, and several other variations (Cardoso et al. 2019). In the 'barrel-stave' model, peptides accumulate on the membrane's surface before inserting themselves into the lipid core. Since AMP molecules interact with both the phosphate groups and the lipid tails, electrostatic and hydrophobic interactions are crucial.

The toroidal pores are characterized by a surface that is coated with phosphate head groups. Due to the limited hydrophobic interaction between AMP molecules and the lipid tails, the primary mode of interaction between AMPs and toroidal pores is predominantly electrostatic in nature. While the toroidal-pore model shares similarities with the barrel-stave model in terms of its process, it distinguishes itself by involving the penetration of peptide helices into the membrane and their subsequent bonding with lipids (J. Li et al. 2017).

The carpet model posits that the outer leaflet exhibits a significant abundance of AMP molecules on its surface, while the inner leaflet does not demonstrate any binding of AMP. The significant difference in charge and surface tension between the two sides

of the membrane will ultimately result in the catastrophic disruption of membrane integrity, causing the release of cytoplasmic substances, ions, and biomolecules (J. Li et al. 2017).

The Detergent-Like model is based on the intercalation of the AMPs into the bilayer. Complex is the interaction of detergents with lipid membranes above the critical micelle concentration (CMC), when AMPs reside in a micellar, aggregated state (Cardoso et al. 2019).

In conclusion, AMPs have shown great potential in preventing implant-associated infections. They have broad-spectrum antimicrobial activity and are less likely to induce bacterial resistance than traditional antibiotics. Further research is needed to optimize the use of AMPs in implant coatings and to evaluate their long-term efficacy and safety in clinical settings.

1.5 Immobilization Approaches to Implant Surfaces

In recent times, there has been a growing interest in the field of biological surface modification as a potential remedy for the difficulties associated with the integration of implants and tissue. In the preceding section, a comprehensive analysis was provided regarding the significance of immobilized biomolecules on implant surfaces in facilitating effective integration. This section will analyze the principles underlying immobilization strategies employed in the biofunctionalization of implant surfaces. The immobilization principle enhances the stability and utility of biomolecules. Nonetheless, the random orientation and structural deformation that occur after attachment may diminish the activity of the biomolecules. To maintain a molecule's biological activity, immobilization techniques must not modify the molecule's structure or function. Chemical and physical immobilizations are the two most common methods for functionalizing implants with biomolecules (Figure 4). As a novel approach, genetically engineered peptides for inorganics (GEPI) promise a more precise biomimetic immobilization procedure and represent an alternative to physical and chemical techniques (Figure 4).

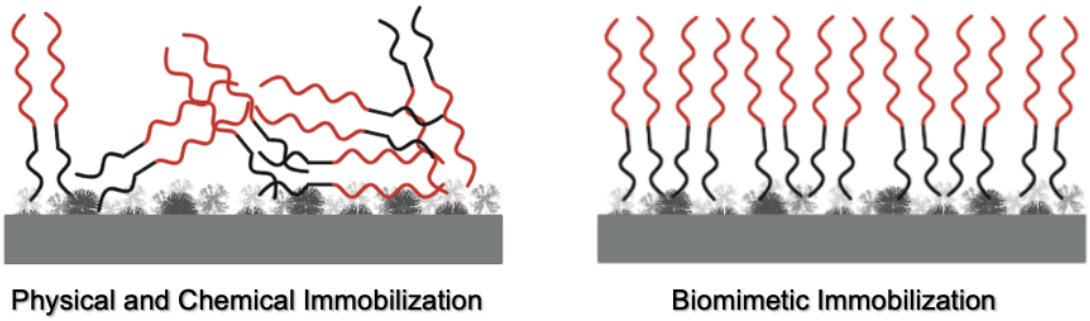

Figure 4. Peptide Immobilization Approaches for Implant Surfaces

1.5.1 Physical Immobilization Approach

The immobilization technique referred to as physical immobilization, or adsorption, is a simple method that can be conducted under mild conditions, resulting in minimal disruption to biomolecules. Nevertheless, the process of biomolecule linking to titanium implants is highly influenced by various experimental parameters, including pH, temperature, and solvent, when the implants are immersed in a solution. Adsorption on surfaces is predominantly attributed to intermolecular forces, encompassing ionic bonding, hydrophobic interactions, and polar interactions. The heterogeneity and arbitrary orientation of the resulting layer primarily stem from the unique optimal conformation of each molecule, which serves to minimize repulsive forces from the surface and previously bound protein during adsorption. It is crucial to highlight that the initial step in chemical immobilization involves the physical adsorption of proteins, while the subsequent stage involves the covalent attachment of proteins to the surface.

In the context of protein adsorption onto a surface, it is imperative that the overall change in free energy is negative, which can be attributed to either enthalpic or entropic factors. During the process of adsorption, many proteins undergo conformational changes, resulting in a weakening of their ordered structural composition. The aforementioned property exhibits an entropic benefit and has the potential to serve as a driving force for adsorption (Norde et al. 1986). The driving force behind adsorption can be attributed to the enthalpic interactions between the protein and the surface. The

interactions that exhibit the highest degree of prominence in various systems include Van der Waals interactions, hydrophobic interactions, electrostatic interactions, and hydrogen bonding (Rusmini, Zhong, and Feijen 2007).

The physical attachment of proteins is directly influenced by the surface properties of inorganic materials. To improve protein adsorption, it may be necessary to modify the surface. Hydrophobicity is a surface property that can be modified through a diverse range of methods. It is hypothesized that hydrophobic interactions between the solid surface and the protein exhibit a greater propensity for protein adsorption compared to hydrophilic interactions. While not universally consistent, this phenomenon is often observed in experimental settings (Rusmini, Zhong, and Feijen 2007). Some researchers determined that fibrinogen preferentially adheres to a hydrophobicity gradient surface (Elwing et al. 1988).

According to the scientific literature, PEG derivatives are commonly employed compounds for the purpose of mitigating protein adsorption on solid surfaces, particularly in the realm of biomedical applications. Surfaces that have been modified with polyethylene glycol (PEG) demonstrate a relatively reduced level of protein adsorption, provided that the PEG chains are of sufficient length and the density of surface molecules is high. The efficacy of the PEG layer in repelling can be interpreted in two distinct manners (Malmsten, Emoto, and Van Alstine 1998; M. Zhang, Desai, and Ferrari 1998). The initial high impedance of proteins is maintained by the dense and thick layer of PEG compounds. Furthermore, it should be noted that there are no variables that drive adsorption. Due to the absence of charge in standard PEG-layers, electrostatic interactions alone are inadequate for facilitating protein adhesion (Burns, Van Alstine, and Harris 1995). PEG molecules can also interact with water molecules, preventing the formation of van der Waals bonds between proteins and surfaces (Stupp, 2010). Given these circumstances, the ability of a protein to adhere to a surface that has been modified with polyethylene glycol (PEG) is significantly hindered, unless it can traverse the PEG layer and access the uncovered surface.

In contrast to methodologies such as covalent coupling, adsorption exhibits a relatively low surface burden. Moreover, there is an uncontrolled desorption of biomolecules from the surface. The method of physical permeation of biomolecules involves the retention of a biomolecule by a barrier without forming a chemical bond. Hence, this approach is highly delicate and can be employed for any biomolecule. Nevertheless, barriers are often delicate, and the loss of biomolecules can occur due to

shredding or degradation. Furthermore, this methodology is commonly utilized in biosensor applications (Scouten, Luong, and Stephen Brown 1995). The attachment of biomolecules to the surface of implants is achieved through the incorporation of said biomolecules into coatings composed of poly (D, L-lactide) (PDLLA), ethylene vinyl acetate (EVAc), and collagen (Welsh et al. 1995; Fischer et al. 2003). Therefore, the manipulation of biomolecule release from the surface of the implant can be feasibly achieved, rendering it a compelling strategy for the immobilization of bone growth factors.

1.5.2 Chemical Immobilization Approach

The process of covalent attachment is extensively employed in the immobilization of peptides, enzymes, and adhesive proteins onto implant surfaces, despite its inherent complexity and time-intensive nature, when compared to alternative methods of immobilization. One of the primary limitations of this technique is the reduction in protein mobility on the surface, which is directly correlated with the probability of novel protein conformations being present. This drawback is particularly pronounced when proteins are immobilized. The potential existence of deleterious monomer residue on the surface of the implant may give rise to concerns regarding the compatibility of the implant with biological systems at the site of insertion. The utilization of physical adsorption techniques, commonly achieved through the dip-coating method to create a layer with desired characteristics, can effectively overcome challenges encountered in the chemical immobilization procedure. The utilization of physical adsorption has the potential to facilitate the elimination of perilous monomer remnants. However, the inherent instability of surface molecules hinders the successful resolution of the binding challenges that arise between materials and immobilized molecules (Tang, Thevenot, and Hu 2008).

Due to limits in chemical and physical modifications, self-assembled monolayers (SAMs) were developed as a technique to precisely manage the density and conformation of a single or several functional groups on a surface (Love et al. 2005). The entire technique for producing SAMs is comprised of two essential components. Before grafting polymerization onto an activated surface, SAMs must first activate the bulk material's

surface. At the conclusion of the two essential steps, SAMs may produce surfaces that are both flat and chemically well-defined (Arima and Iwata 2007). Obtaining densely packed, well-ordered functions on the surface that approach thermodynamic equilibrium is another advantage of SAMs

Generally, surface acoustic waves (SAWs) encompass functionalities related to pattern and density control. The terminal group that has been chosen can also be utilized as a site for further surface functionalization. The utilization of self-assembled monolayers (SAMs) has been employed to investigate cellular responses in vitro and inflammatory and foreign body reactions in vivo, as well as various other processes associated with implanted biomaterials. This approach has facilitated the understanding of the impact of specific functional groups on particular processes (Faucheux et al. 2004). Nevertheless, there exist restrictions regarding the categories of substances that are compatible with self-assembled monolayers (SAMs). Gold and silver are the most frequently employed substances for rapid functionalization of self-assembled monolayers (SAMs). In order to generate reactive groups, such as amino or aldehyde groups, these surfaces can be derivatized (Sakiyama-Elbert and Hubbell 2003).

1.5.3 Genetically Engineered Peptides for Inorganics

Molecular recognition, which refers to the specific interactions between biomolecules, plays a crucial role in facilitating the various molecular processes necessary for biological functions within living systems. In order to achieve the accurate development of biologically compatible, molecularly-customized soft interfaces on solid surfaces, it is imperative to establish targeted biological interactions between the solid materials and biological components. Solid-binding peptides offer more extensive possibilities for surface biofunctionalization compared to traditional chemical methods that depend on inflexible covalent bonds for attaching molecules to surfaces. The lack of capability exhibited by chemical methods in achieving spatial organization and orientation control of biomolecules on support surfaces poses a significant challenge (Yucesoy et al. 2020). In addition, non-specific binding reduces the functionality or stability of biomolecules.

There exist two prerequisites for addressing the aforementioned issues. The immobilization technique must possess a tailored adhesion to the selected solid surface, and it should also be flexible enough to accommodate the attachment of a chemically or genetically affixed probe. Additionally, it should function as an intermediary between the biological molecule and the solid surface. The application of directed evolution methods that leverage genotype-to-phenotype relationships is employed for the purpose of identifying solid-binding peptides, also referred to as genetically engineered peptides for inorganic materials. These peptides exhibit exclusive binding to solid substances through molecular recognition (Yucesoy et al. 2020).

Within this particular segment, the peptide undergoes a process of self-organization on the surface, adopting a conformation that aligns with the structure of the solid lattice. Solid-binding peptides possess a unique biological advantage as they serve as modular building blocks for coupling biological and synthetic elements at the interfaces of biosolids. Through the utilization of the diverse capabilities of biology, it is feasible to manipulate chimeric molecules that possess inherent multifunctionality, thereby demonstrating biofunctional molecular entities including enzymes, cofactors, antimicrobial peptides, antibodies, nucleic acids, and molecular probes that specifically target biomarkers (Figure 5) (Yucesoy et al. 2020). As a example, gold binding, titanium binding, and hydroxyapatite binding peptides were studied in detail and their binding properties were confirmed (Khatayevich et al. 2010; H. Yazici et al. 2013).

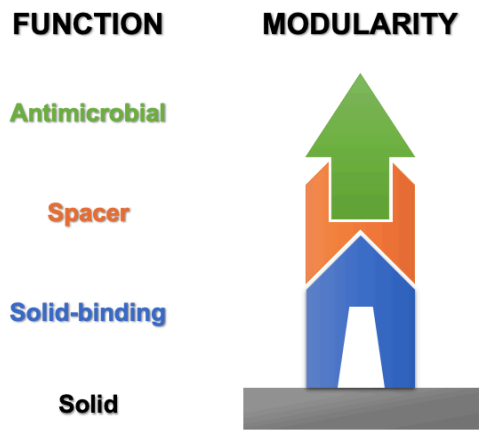

Figure 5. Combinatorial Design of Chimeric Constructs (Yucesoy et al. 2020)

Implants can have their biocompatibility, functionality, and durability enhanced by biofunctional coatings and engineered protective molecular biofilms. These coatings and biofilms can be designed to interact in a specific manner with biological systems, to add specific functionality to the implant, or to protect the implant from biological degradation.

Biofunctional coatings can be used to improve the biocompatibility of implants by making them less likely to cause an immune response or be rejected by the body, add specific functionality to implants by enabling them to bind specific molecules or to release drugs or other therapeutic agents in a controlled manner and protect implants from biological degradation by inhibiting the growth of bacteria and other microorganisms on the implant surface (H. Yazici et al. 2013). Engineered protective molecular biofilms can be used to provide a physical barrier between the implant and the surrounding tissue, preventing the migration of cells and proteins to the implant surface, releasing antimicrobial agents that kill bacteria and other microorganisms that may come in contact with the implant, and promoting the growth of tissue around the implant, which can help to anchor the implant in place and improve the implant's long-term success (H. Yazici et al. 2013; Yucesoy et al. 2015; Hilal Yazici et al. 2016).

As a conclusion, biofunctional coatings and engineered protective molecular biofilms are a promising new technology for improving the performance of implants. By using these coatings and biofilms, new implants can be create that are more biocompatible, functional, and durable.

CHAPTER 2

MATERIAL AND METHODS

2.1. Aim of Thesis

The purpose of this study was to design functional chimeric peptides using antimicrobial peptides and hydroxyapatite binding peptides in order to provide an antimicrobial effect to hydroxyapatite-coated titanium dental implants. Before constructing this design, cariogenic AMPs were chosen based on the available literature and databases. The secondary structure analysis was then performed to confirm that the selected AMPs had been chimerized with the hydroxyapatite-binding peptide and maintained their original structures. In secondary structure analysis, chimeric peptides with the minimum structural change were analyzed and promising candidates were chosen.

3-Step analyzing approach determined, including secondary structure analyze, solubility analyze and conformational analyze, to analyze created chimeric peptides (Figure 6). Based on amino acid sequence, promising candidates selected by secondary structure analysis were subjected to solubility analysis as hydrophilic or hydrophobic. In the solubility analysis, promising candidates for chimeric peptides within the optimal range were identified. Finally, promising candidates that came up from the secondary structure and solubility analysis were simulated using molecular dynamics according to the least conformational change.

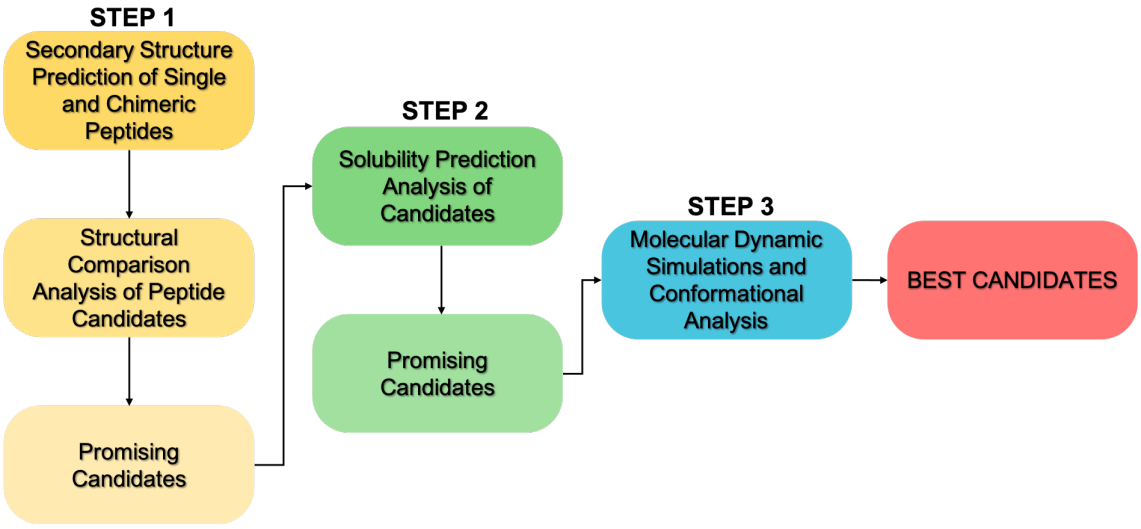

Figure 6. 3-Step Approach to Analyze Designed Chimeric Peptides

2.2 Peptide Selection and Chimerization

When oral pathogens are considered, implant-failure-causing bacteria such as Streptococcus mutans come to the forefront (Forssten, Björklund, and Ouwehand 2010). In this context, antimicrobial peptides have emerged as viable alternatives to traditional antibiotics for the treatment of oral bacterial infections. Using synthetic combinatorial peptide libraries, novel antimicrobial peptides against Streptococcus mutans, a prominent cariogenic pathogen, and other oral pathogens, particularly in the buccal cavity, have been identified (Song et al. 2014). Many studies have determined the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of these peptides, demonstrating their potent antimicrobial activity (Franca et al. 2014; Yucesoy et al. 2015; Hilal Yazici et al. 2016). Cariogenic antimicrobial peptides have demonstrated tremendous potential for preventing dental caries and controlling the development of cariogenic bacteria in the oral cavity.

Therefore, antimicrobial peptides effective against cariogenic bacteria were selected using literature and databases, taking into account the low minimum inhibitory concentration (MIC) value. Also, hydroxyapatite binding peptide was chosen as the solid

binding peptide, since it was aimed to impart antimicrobial effect to hydroxyapatite coated implants.

After peptide selections, selected antimicrobial peptides and hydroxyapatite binding peptide were chimerized with GGG spacer (Figure 7). The purpose of using the GGG spacer here is to provide lateral mobility of the designed chimeric peptides (Yazici et al. 2016). In addition, chimerization was applied to bind the hycroxapatite binding peptide to the N-terminus and C-terminus of each antimicrobial peptide.

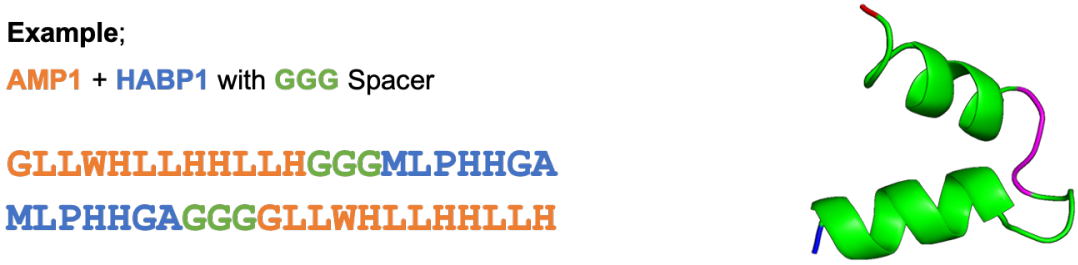

Figure 7. An Example for Chimeric Peptide Creation

2.3. Secondary Structure Prediction of Peptides

Peptide secondary structure prediction is the computational or experimental determination of the local conformation of the peptide backbone, which comprises -helices, -sheets, twists, and disordered portions with specified dihedral angles and H-bond patterns. Several approaches, including Chou-Fasman algorithms, the GOR method, neural networks, and deep learning methods, are utilized for secondary structure prediction (Faraji et al. 2022). Understanding peptide-protein, peptide-membrane, and peptide-DNA interactions, folding from the sequence, and estimating their probable function requires the prediction of peptide secondary structure (John et al. 2019; Matveev, Safronov, and Kazanov 2021).

In bioinformatics, secondary structure prediction algorithms are commonly used to predict the secondary structure of proteins. Self-optimize prediction method (SOPMA), Porter tool, GOR4, SOPM, SOPMA 29, Secondary Structural Content Prediction (SSCP method-I) server, and Mfold web server are some regularly used tools. PSIPRED is regarded the best technique for predicting secondary structures. Additionally, PEP-FOLD is a cutting-edge online computational system for predicting the secondary structure of proteins and peptides (Lamiable et al. 2016).

PEP-FOLD is a tool that is used to predict the three-dimensional structure of peptides and small proteins based on their amino acid sequences. The program employs an algorithm based on the notion of de novo protein folding, which includes predicting the shape of a peptide or protein that is most energetically advantageous. PEPFOLD predicts the structures of peptides and small proteins using a mix of lattice-based and ab initio approaches. The PEPFOLD method is based on the notion of energy minimization, which entails locating the shape of a peptide or protein with the least amount of energy. The program samples the conformational space of the peptide or protein using a Monte Carlo simulation and identifies the most energetically acceptable configuration. In addition, the algorithm uses a knowledge-based technique that combines information from known protein structures to increase the accuracy of its predictions.

In this section, HABP1 and antimicrobial peptides are modeled using the PEPFOLD online platform. In addition, the chimeric peptides created by combining of these peptides, were modeled and their structural changes relative to the originals were investigated. RMSD analysis was done to determine the conformational change, and the findings were analyzed.

2.4 Solubility Prediction of Peptides

Peptide solubility can be affected by peptide sequence, length, conformation stability, and environmental conditions such as temperature, pH, and ionic strength. The secondary structure of a peptide can influence its tendency to aggregate. Researchers discovered that peptides with a significant propensity to form α-helical secondary

structure were more likely to assemble into amyloid fibrils than unstructured or "random coil" peptides (John et al. 2019).

Peptide solubility has been extensively studied using computational techniques. Hydrophilicity refers to a peptide's capacity to interact with water molecules, whereas aggregation propensity refers to a peptide's inclination to form aggregates or amyloid fibrils. Various computer techniques, including TANGO, AGGRESCAN, FoldAmyloid, AMYLPRED, and CamSol, have been developed to predict the solubility of peptides (Aronica et al. 2021). These algorithms anticipate the tendency of a peptide to form amyloid fibrils based on a variety of factors, including the amino acid sequence, the secondary structure, and the solvent accessibility. CamSol is a computer approach used to estimate the solubility of proteins and peptides based on their sequence information. CamSol predicts solubility changes resulting from mutations and incorporates the contribution of various physicochemical properties, such as hydrophobicity, structural propensities, and electrostatics, at the level of individual residues considered within local motifs and in the context of the entire sequence (Oeller et al. 2023).

CamSol provides both Intrinsic and Structurally Corrected solubility analyses (Figure 8). CamSol Intrinsic analysis utilizes simply the amino acid sequence of the peptide, however Structurally Corrected analysis employs the secondary structure of the peptide. In the intrinsic concept, it only analyzes at a radius of seven amino acid window, while the Structurally Corrected concept providing the relationship of amino acids in the desired radius. Each concept provides a value for each residue as a result of the analysis. These values are classified as 1 or more hydrophilic, 0 to 1 hydrophilic tendency, 0 to -1 hydrophobic tendency, and -1 or less hydrophilic.

The radius value for each peptide was calculated based on the 3.8-angstrom value between the two alpha carbons in order to make the structurally corrected method suitable for our study. Then, a limit was determined by examining just AMPs to identify what the range should be when AMPs are evaluated in their chimeric form. After determining the limit, chimeric peptides were examined based on this limit, and the best candidates were identified.

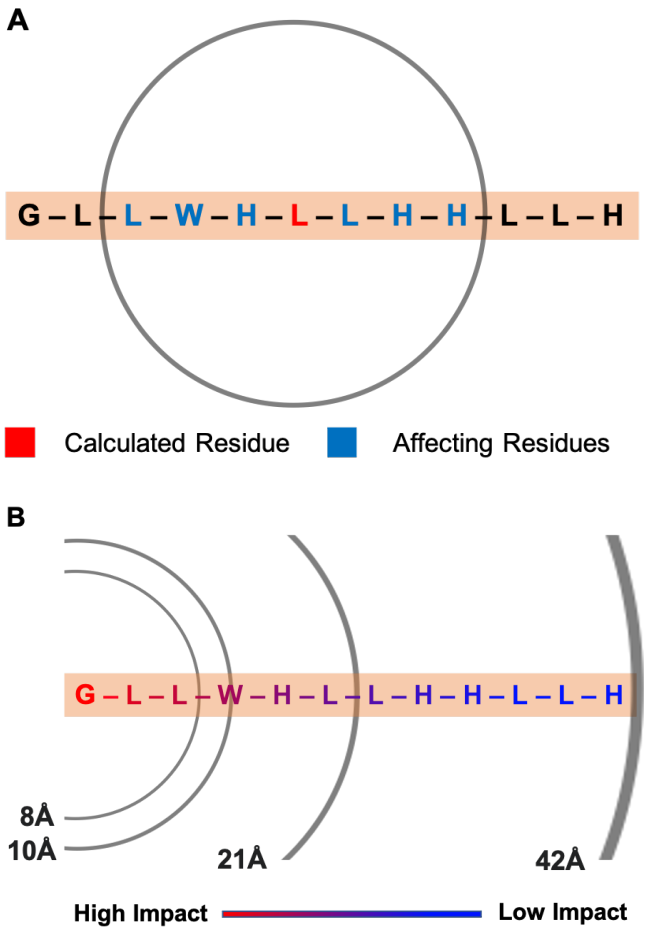

Figure 8. CamSol Intrinsic Concept and CamSol Structurally Corrected Concept.

2.5 Molecular Dynamics Simulation of Peptides

Molecular dynamics simulations (MD) are a powerful tool for studying the behavior of molecules and materials at the atomic level. MD simulations involve solving the equations of motion for a system of interacting particles, typically using classical mechanics.

The fundamental principle that underlies a molecular dynamics (MD) simulation is relatively simple. It is feasible to determine the forces exerted on individual atoms within a biomolecular system, such as a peptide/protein immersed in water and potentially enclosed by a lipid bilayer, by utilizing the coordinates of all the atoms involved (Badar

et al. 2022). By employing Newton's equations of motion, molecular dynamics (MD) is capable of estimating the temporal variation in the spatial position of individual atoms. In the context of temporal progression, the advancement occurs by iteratively computing the forces exerted on individual atoms and subsequently employing these forces to modify the position and velocity of each atom (Adcock and McCammon 2006). The trajectory obtained can be described as a three-dimensional animation that visually represents the atomic-level arrangement of the system at various time points within the simulated time interval.

The simulations can be used to investigate a wide range of phenomena, including protein folding, functional dynamics in biomolecules, and protein-protein binding (Freddolino et al. 2010; Markwick and McCammon 2011; Sun et al. 2017). MD simulations are a valuable tool for studying peptides. They can provide information about the structure, dynamics, and interactions of peptides that cannot be obtained from other experimental methods. This information can be used to understand how peptides function in biological systems and to design new peptides with specific properties (Tsai et al. 2009).

In the light of this information, promising candidates from secondary structure analysis and solubility analysis, a water box was created using sodium chloride ions and water molecules to neutralize the medium (Figure 9). This created system has been simulated for 35 nanoseconds for each candidate. Depending on the time and considering the conformational change, the candidates were analyzed and the best candidates were decided.

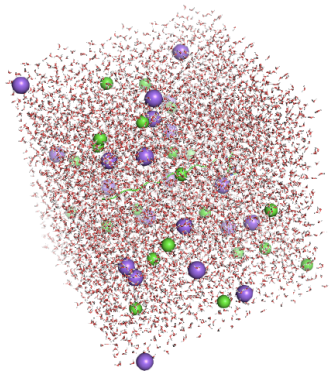

Figure 9. An Example of Waterbox with a Peptide.

CHAPTER 3

RESULTS AND DISCUSSION

Here, in addition to the currently biocompatible implant coatings, a biomimetic coating design providing resistance to infection has been performed. In this context, in addition to the biocompatible hydroxyapatite-coated titanium implants, antimicrobial peptides were taken into consideration and chimeric peptides that could provide antimicrobial resistance were designed. Computationally, secondary structure analysis, solubility analysis, and conformational change analysis were performed to examine whether these formed chimeric peptides could preserve their antimicrobial properties. Conformational analyzes of promising candidates obtained from secondary structure and solubility analysis were also performed and the most suitable candidates were decided.

3.1. Peptide Selection and Chimerization

The following is a list of antimicrobial peptides that are effective against cariogenic bacteria and were chosen based on the literature and databases, taking into account the low MIC value. The table contains the sequence, MIC value, MW value, and pI values of the peptides (Table 3).

Table 3. List of Antimicrobial Peptides Effective to Cariogenic Bacteria

Number	Sequence	MIC Value		MW	pI	Source
AMP1	GLLWHLLHH LLH	S.mutans ATCC700610 GS-5 COCC32-3	4,5μM/L 5,3μM/L 2,6μM/L	1488.8	7.1	(Wang et al. 2017; W. Jiang et al. 2018; Afshar et al. 2021)
AMP2	KIFGAIWPLA LGALKNLIK	S.oralis S.sanguinis S.mutans S.sobrinus E.coli	7,5μM/L 7,5μM/L 60μM/L 7,5μM/L 32 μM/L	2066.6	10.3	(Da Silva et al. 2013)
AMP3	WKLLRKAWK LLRKA	S.mutans S.salivarius S.sobrinus	8.00μM/L 16.00μM/L 32.00 μM/L	1810.3	12.0	(Luo et al. 2021)
AMP4	GKLIWKLLRK AWKLLRKA	S.mutans S.salivarius S.sobrinus	16.00μM/L 11.20μM/L 16.00 μM/L	2221.8	12.0	(Luo et al. 2021)
AMP5	KKVVFKVKF K	S.mutans S.sobrinus S.sanguinis S.gordonii	0.0625 mg/mL 0.125mg/mL 0,1μM/L 0,3μM/L	1250.6	10.6	(Liu et al. 2011)
AMP6	KNLRIIRKGIH IIKKY	S. mutans UA159 25175	12.1 ± 4.5 μM 14.8 ± 2.0 μM	1993.5	11.2	(Kaplan et al. 2011)
AMP7	FKIGGFIKKL WRSLLA	S.mutans S.sobrinus S.gordonii P.gingivalis	8-16μM 8μM 8-16μM 16μM	1877.3	11.2	(Chen et al. 2017)
AMP8	RIWVIWRR	S.mutans S.sanguinis S.sobrinus	16μg/mL 16μg/mL 16μg/mL	1184.4	12.3	(Ding et al. 2014)
AMP9	IKKILSKIKKL LK	C.albicans S.mutans S.salivarius S.sanguinis	6.25μM 3.13μM 6.25μM 6.25μM	1553.0	10.7	(Shang et al. 2014)
AMP10	LRWWLWKLL RRMR	S. Mutans ATCC25175 S. Sobrinus ATCC33478 S. Gordonii ATCC10558 P. gingivalis	3.3μM 3.3μM 3.3μM 3.3 μM	1913.4	12.4	(Liang et al. 2019)
AMP11	LKLLKKLLKL LKKL	S.epidermidis E.coli S.mutans	1 μg/mL 32 μg/mL 16 μg/mL	1692.3	10.7	(Yucesoy et al. 2015; Yazici et al. 2016)
AMP12	KWKRWWW WR	S.epidermidis E.coli S.mutans	8 μg/mL 16 μg/mL 64 μg/mL	1517.8	12.0	(Yucesoy et al. 2015; Afshar et al. 2021)

Considering the aim of the thesis, cariogenic peptides effective on microorganisms such as S. Mutans and S. epidermidis, which are prominent in implant infection, were investigated. In this context, peptides were selected considering the strains they act on, low MIC values and sequence length. Tests with a low MIC value give the value in which a small amount of peptide shows the highest effect. Because of their low cost and easy synthesis, peptides with short sequence lengths came into prominence.

As a result of the chimerization of hydroxyapatite binding peptide and each antimicrobial peptides 24 chimeric peptide obtained.

3.2. Secondary Structure Prediction

Secondary structure analysis was performed to analyze whether AMPs and HABP1-generated chimeric peptides (Straight and Reverse) could retain their original structure (Figure 10). The structural change was quantified by separately aligning the two portions of the chimeric peptide with the peptides' original states. AMP2, AMP5, AMP6, AMP7, AMP8, and AMP12 were unable to maintain their original structures in chimeric form, whereas AMP1, AMP3, AMP4, AMP9, AMP10, and AMP11 predominantly maintained their original structures (Figure 10 A,B).

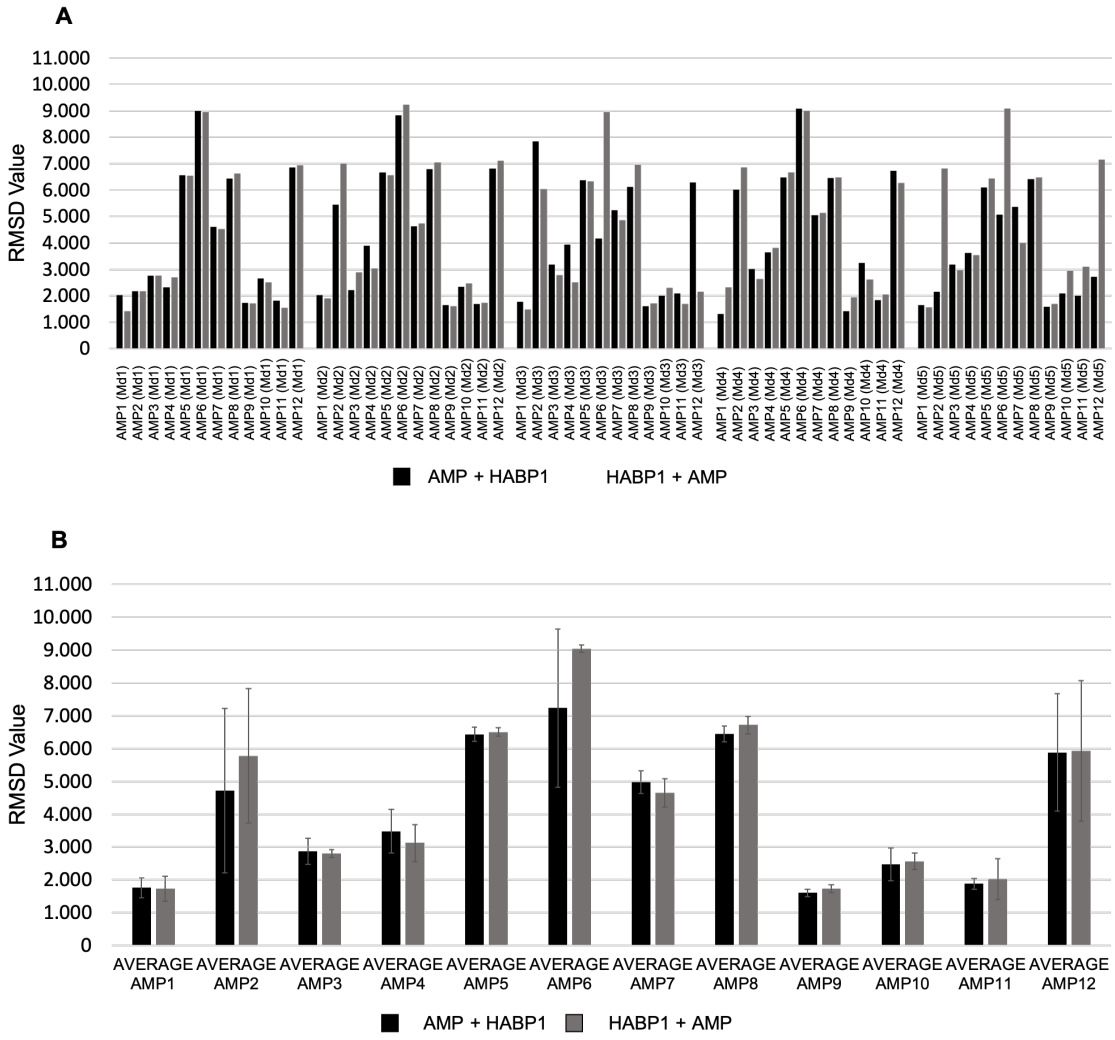

Figure 10. Investigation of whether the structural change is preserved in the chimeric structure by comparing the antimicrobial parts of chimeric peptides with the models in which the peptide is alone A) Root mean square deviation data of antimicrobial peptides B) Average data of root mean square deviation analysis of antimicrobial peptides

In the Secondary structure analysis for HABP1, the structural change was quantified by aligning the HABP1 portion of the chimeric peptide with its native form.

As a consequence of the analysis, the arithmetic mean of the values and the rate of change were calculated (Figure 11). All chimeric peptides exhibited comparable rates of change in HABP1 peptide, based on the average data (Figure 11A). Considering the AMP and HABP1 analyses, intriguing candidates were identified by examining the AMP

changes. As a consequence of the analysis, promising candidates AMP1, AMP9, and AMP11 were identified (Figure 11B).

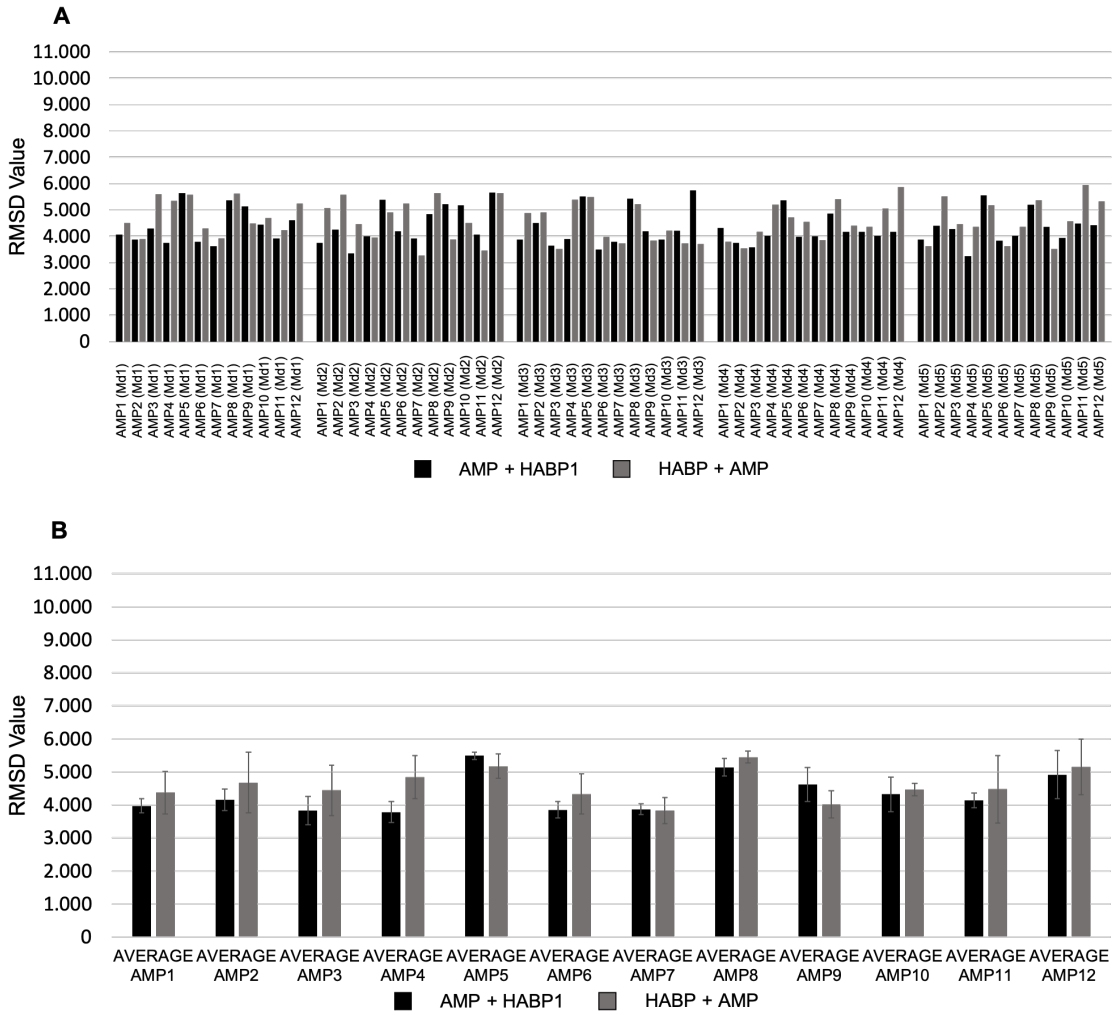

Figure 11. Investigation of whether the structural change is preserved in the chimeric structure by comparing the hydroxyapatite binding parts of chimeric peptides with the models in which the peptide is alone A) Root mean square deviation data of antimicrobial peptides B) Average data of root mean square deviation analysis of antimicrobial peptides

In terms of this study, tools for predicting the secondary structure of peptides offer numerous benefits. By predicting the secondary structures of peptides, we can obtain

insight into their functional mechanisms. Predicting peptide secondary structures is also an important intermediate step in predicting 3D or tertiary structures, which, along with the secondary structure, are crucial determinants of peptide bioactivity (Y. Jiang et al. 2023). In addition, these tools are open access and fast results systems. Peptide secondary structure prediction can be used to predict novel peptide secondary structures if the models attain a robust and promising performance as we do. In this study, we used the PEPFOLD tool, since it focused specifically on peptides, but there are many tools that make predictions (Aronica et al. 2021). In order to analyze the structural change, secondary structures, and RMSD values were considered. RMSD (root mean square deviation) quantifies the distance between two coordinate systems. RMSD is frequently used to compare the structures of two distinct peptides or the structure of a peptide to a theoretical model in the context of peptides. To calculate RMSD, all atom coordinates in one peptide are compared to all-atom coordinates in the other peptide. The squared distances between each pair of elements are then averaged. The RMSD is the square root of this average. A smaller RMSD indicates that the two peptide structures are more similar. A RMSD of zero would indicate that the structures of the two peptides are identical. RMSD is a potent instrument for analyzing peptides, but it should be noted that it is not an ideal measure of similarity. Several factors can influence the RMSD between two peptides, including the length of the peptides, the number of amino acid substitutions, and the prevalence of disordered regions.

3.3. Solubility Prediction

In the solubility analysis, the sequence of each chimeric peptide was analyzed. Prior to determining whether or not the chimeric peptides are suitable, standards were established. In order to provide these standards, the lower limit and optimal range of solubility for each AMP were determined by conducting a solubility analysis (Figure 12).

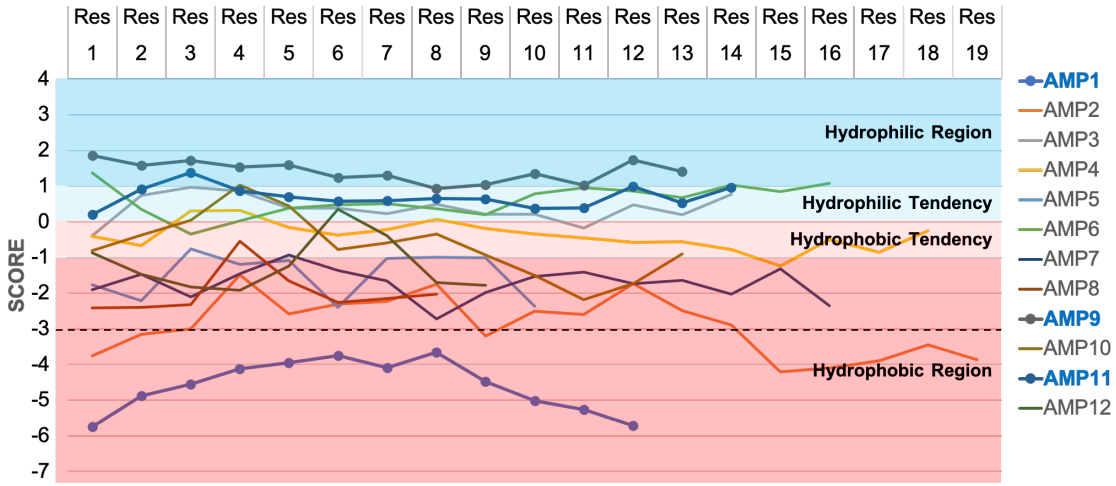

Figure 12. Determination of Solubility Limit and Range for Chimeric Peptides

While the minimum threshold was set at -3, the optimal range was defined as -3 and above. After analyzing the chimeric peptides in light of these standards, intriguing candidates were identified. Although straight and reverse AMP1 chimeric peptides are at the lower limit, chimeric structures have been identified as promising candidates since AMP1 is known to be highly effective in the literature (Figure 13). In the analysis of the chimeric forms of AMP9 and AMP11, the values were found to be above the limit and the ideal range (Figure 14, 15). Consequently, candidates for secondary structure analysis also demonstrated significant solubility results.

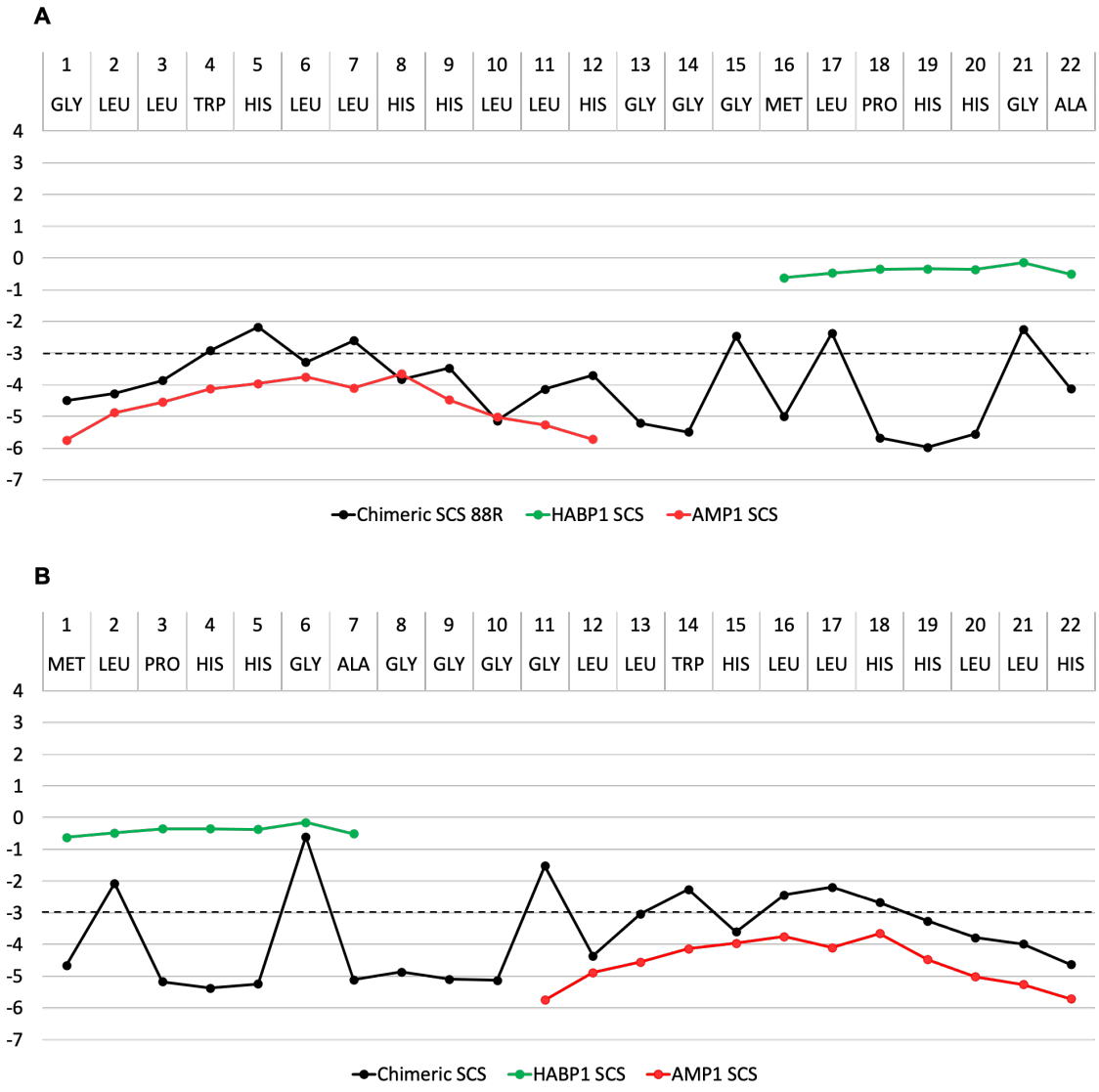

Figure 13. Solubility analysis of Chimeric AMP1 Peptides A) Straight Chimeric Peptide Solubility Scores B) Reverse Chimeric Peptide Solubility Scores

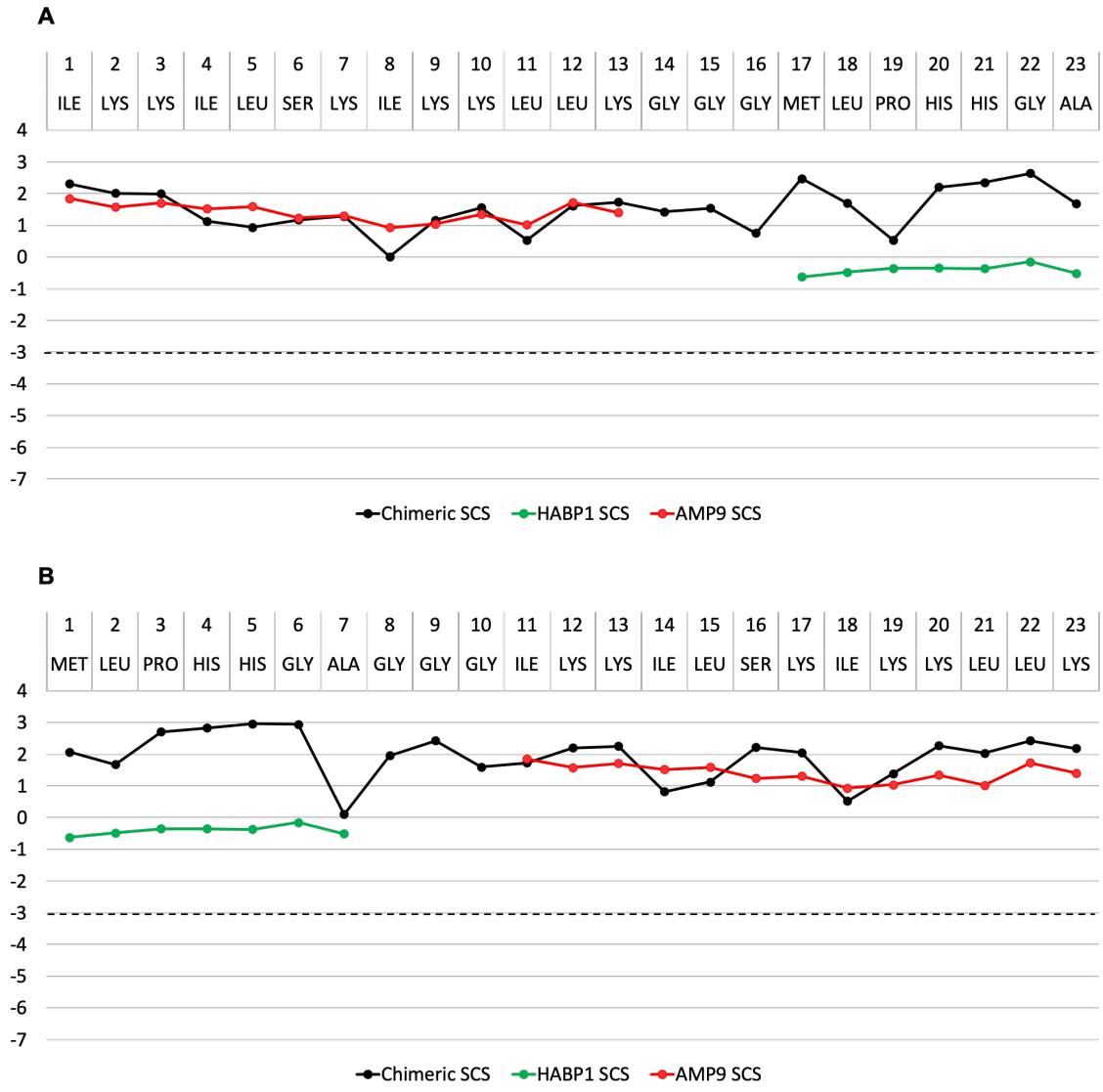

Figure 14. Solubility analysis of Chimeric AMP9 Peptides A) Straight Chimeric Peptide Solubility Scores B) Reverse Chimeric Peptide Solubility Scores

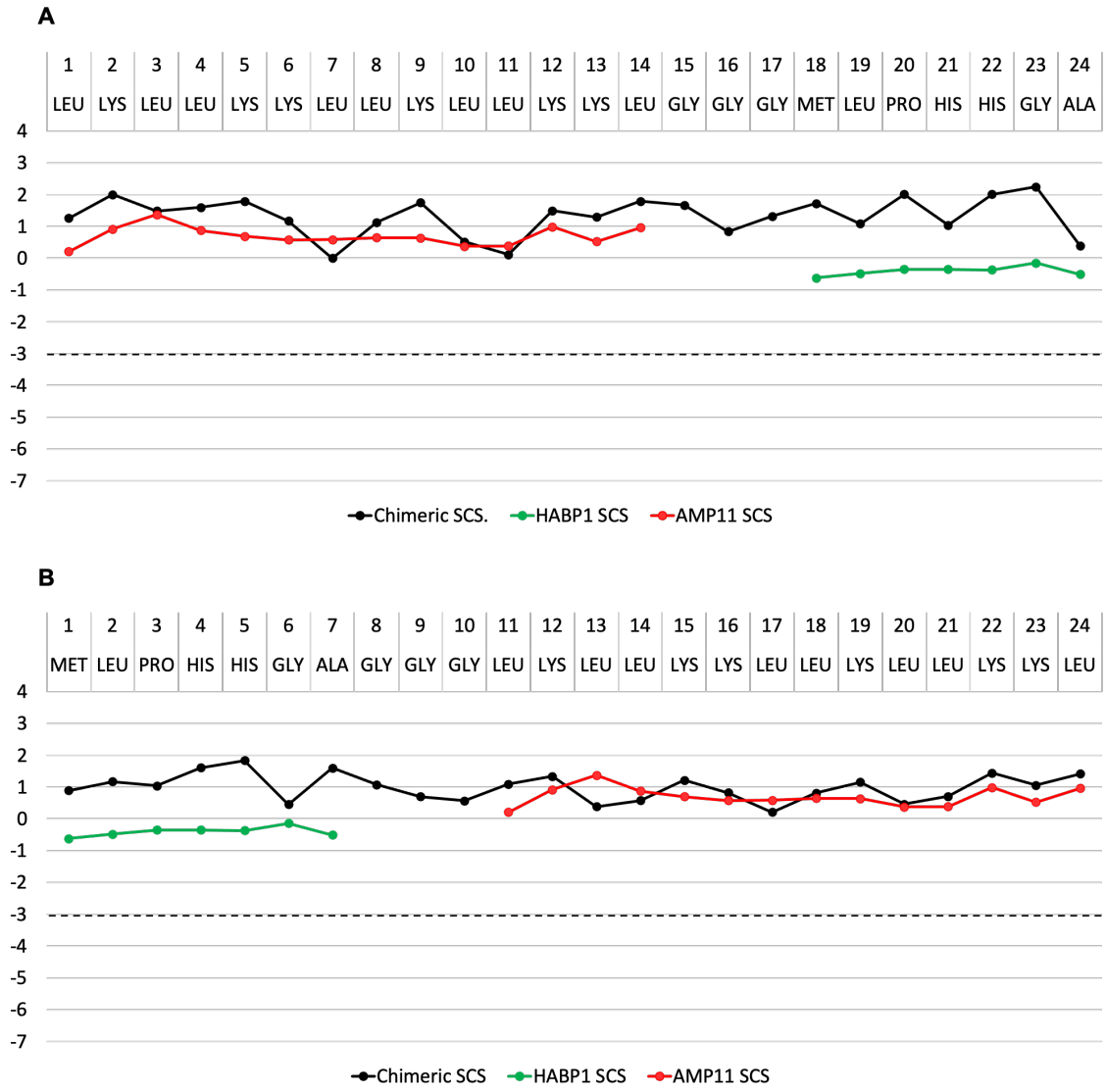

Figure 15. Solubility analysis of Chimeric AMP11 Peptides A) Straight Chimeric Peptide Solubility Scores B) Reverse Chimeric Peptide Solubility Scores

When the implants are coated with the peptide, they are covered by the solution dipping technique, so they must be soluble. In addition, peptides can lose their properties by entering hydrophobic-hydrophobic interactions when they are extremely hydrophobic. In particular, antimicrobial peptides have amphipathic properties and provide their antimicrobial effects depending on this property.

MD simulations are a standard for predicting conformational behaviour. With these simulations, linear secondary structures of single AMP1, AMP9, AMP11 and chimeric candidates were formed. Afterwards, a waterbox was created using water molecules and ions with the peptides in the center. The addition of ions here is to neutralize the medium. Finally, simulations of 35 ns were performed.

3.4. Conformational Analysis of Designed Peptides

For conformational analysis, simulations of promising candidates from secondary structure/solubility analysis were conducted using molecular dynamics. For 35 nanoseconds, simulations were conducted for every single and chimeric peptide (Figure 16, 18, 20). After that, secondary structure models were determined as the RMSD score of the single peptides, i.e., from the highest conformational change sites. Using these reference models as reference points for simulations of chimeric peptides, a similarity analysis was conducted. As a consequence of this analysis, chimeric peptides were analyzed by examining the time-dependent stability of regions with a low RMSD score, i.e. regions that undergo similar conformational change. Aligning the stability and similarity simulations with secondary structures from the stable region confirmed the analysis. The secondary structures collected in the average region were aligned and the analysis was completed for the unstable candidates.

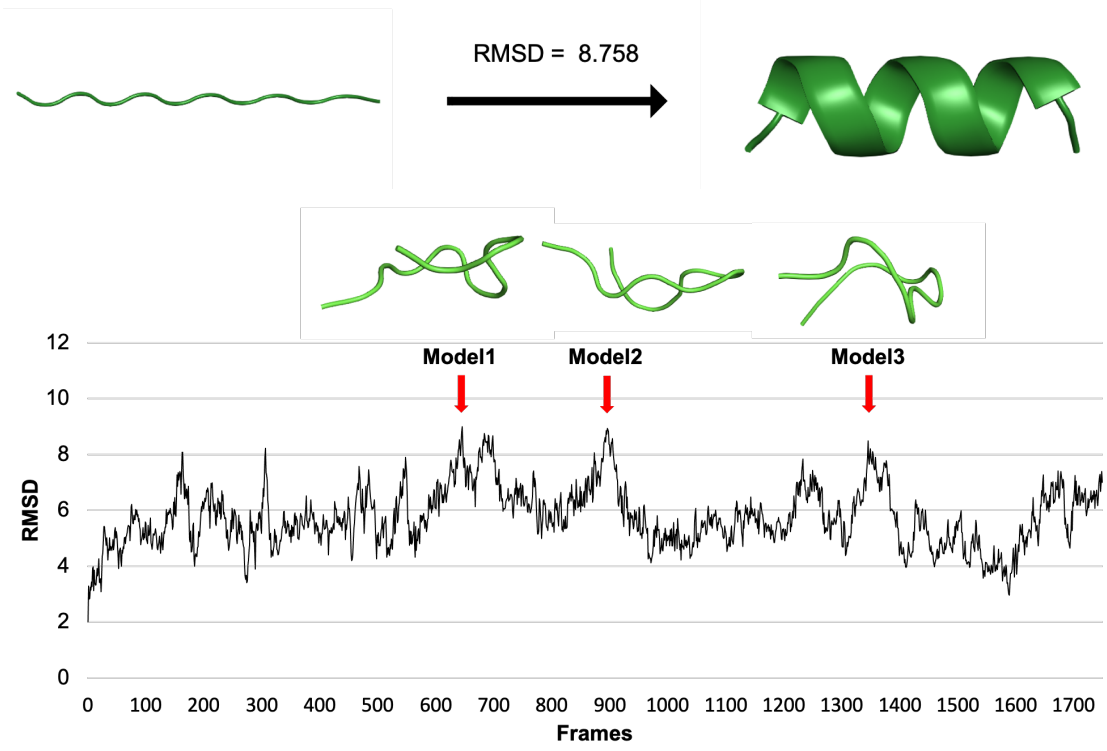

Figure 16. AMP1 Molecular Dynamics Simulation at 35ns to Identify Reference Models for AMP1 Chimeric Peptides Simulation Analysis.

When the linear AMP1 chimeric peptide was analyzed, a stable region of approximately 20 nanoseconds was observed. The secondary structures selected from a single AMP1 simulation nearly matched the secondary structures from the stable region (Figure 17A). Analyzing the reverse AMP1 chimeric peptide for 35 nanoseconds revealed no stability. Due to the absence of a stable region, conformational analysis was conducted by aligning the secondary structure of the average region with the secondary structure of a single AMP1 simulation. The analysis revealed that the secondary structure of the reverse AMP1 chimeric peptide simulation did not match that of the single AMP1 simulation (Figure 17B).

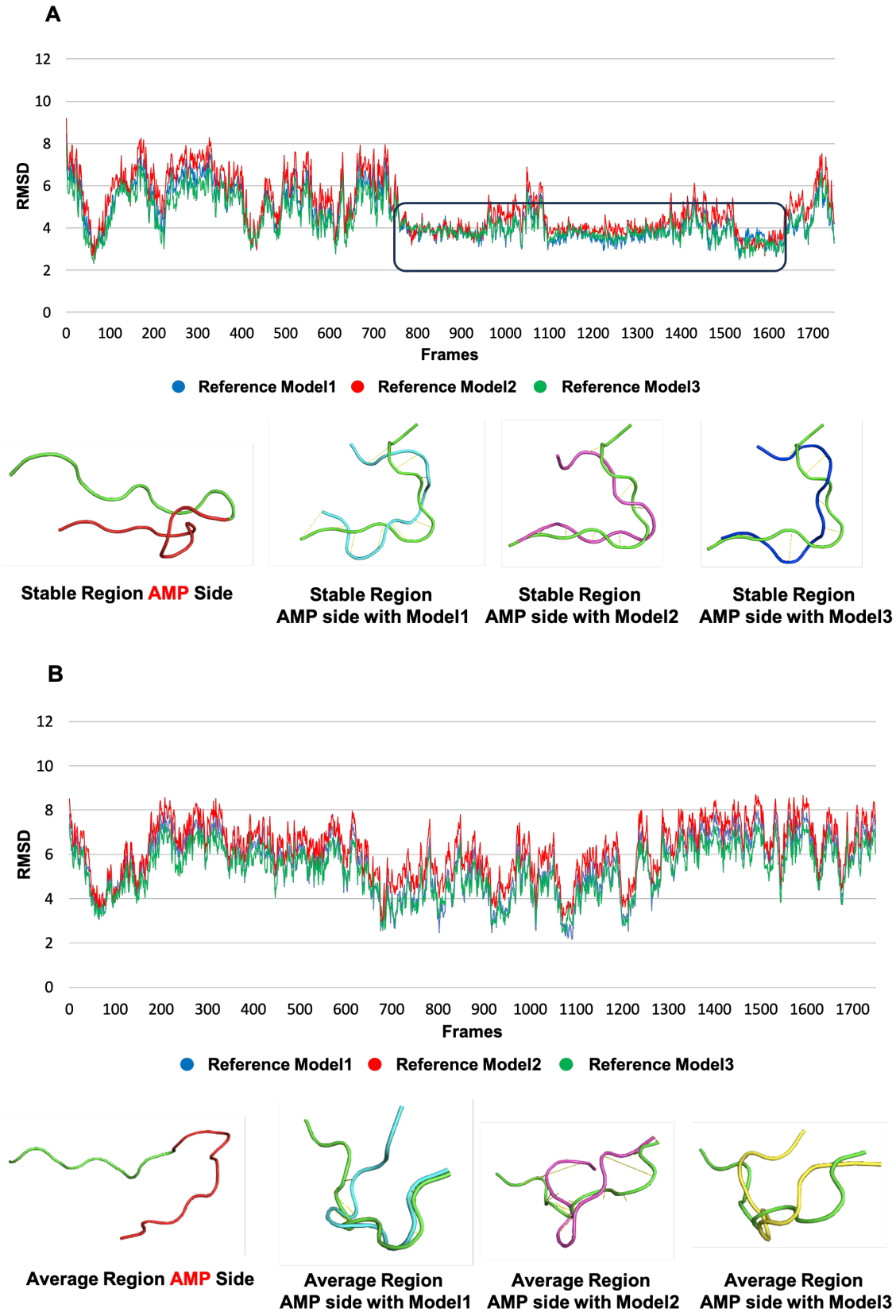

Figure 17. AMP1 Chimeric Peptides Simulation Analysis with Reference Models A) Linear Straight AMP1 Analysis B) Linear Reverse AMP1 Analysis

The same analyses were conducted on both the straight and reverse AMP9 chimeric peptides (Figure 18). The simulation of a straight AMP9 chimeric peptide revealed a stability of approximately 4 nanoseconds. By aligning the secondary structure of the stable region with the models from a single AMP9 simulation, structural similarity was analyzed (Figure 19A). As a consequence of the analysis, it was determined that the structural similarity was almost matching, but that it was not stable. Analyzing the reverse AMP9 chimeric peptide revealed a stability of approximately 12 nanoseconds. Aligning the secondary structure from the stable region and the secondary structure from a single AMP9 simulation revealed that the structures were comparable (Figure 19B).

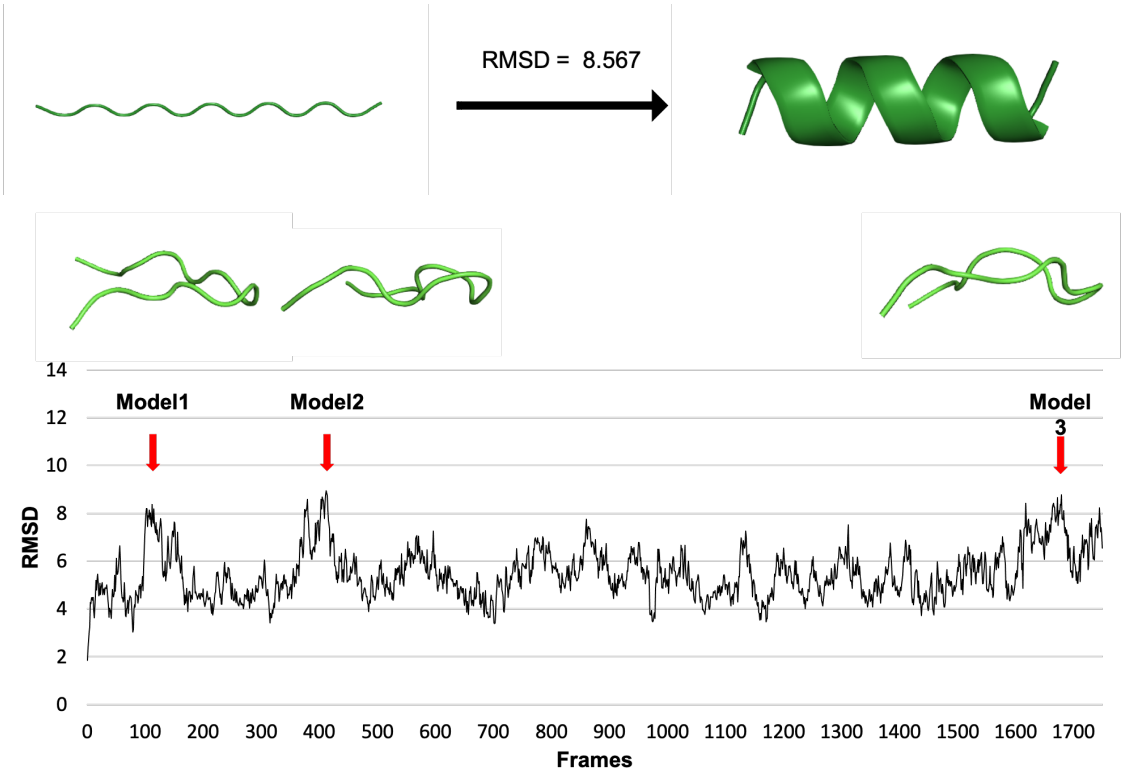

Figure 18. AMP9 Molecular Dynamics Simulation at 35ns to Identify Reference Models for AMP9 Chimeric Peptides Simulation Analysis.

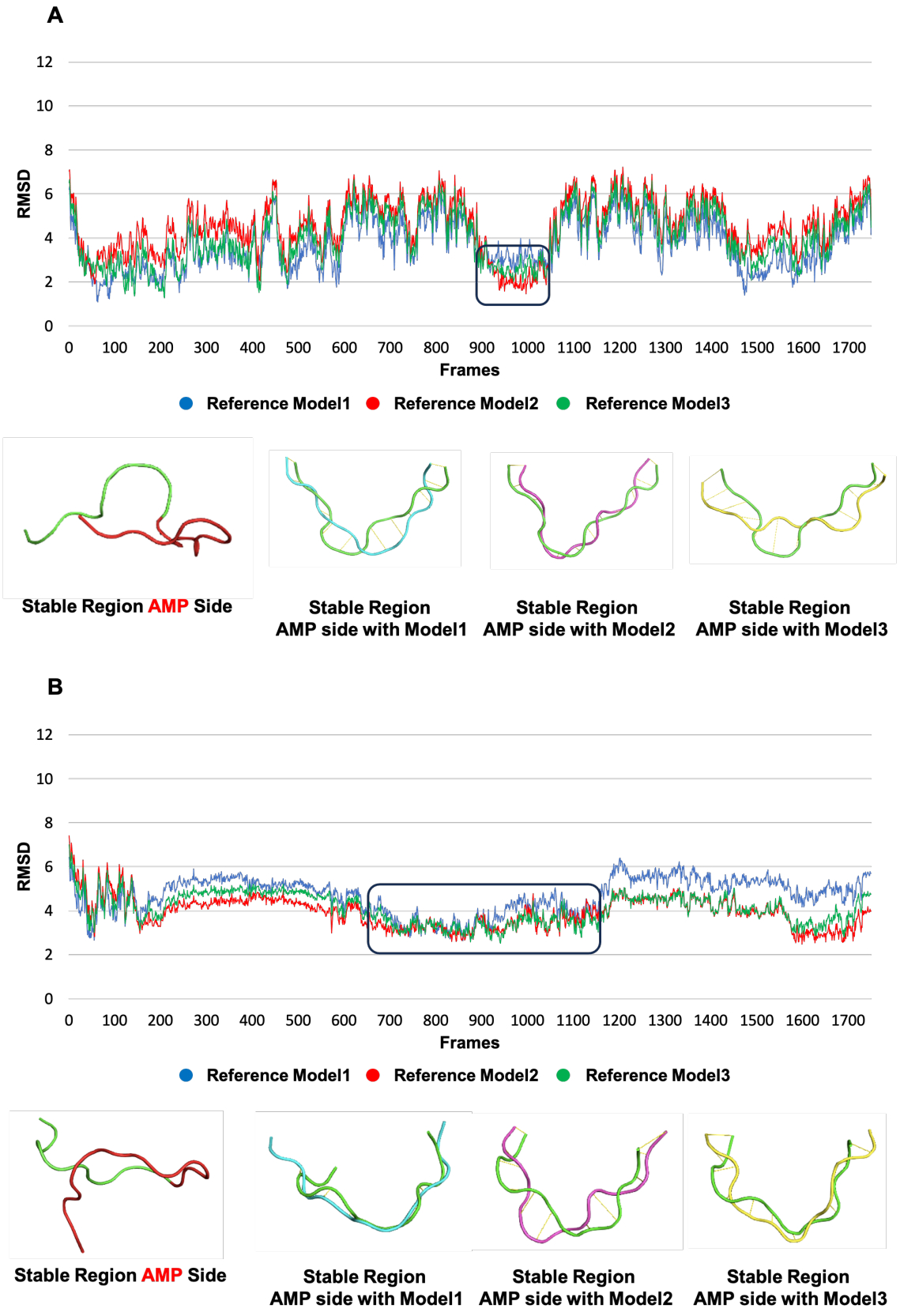

Figure 19. AMP9 Chimeric Peptides Simulation Analysis with Reference Models A) Linear Straight AMP9 Analysis B) Linear Reverse AMP9 Analysis

Finally, straight and reverse AMP11 chimeric peptides were analyzed (Figure 20). The simulation of the straight AMP11 chimeric peptide revealed no stability. By aligning the secondary structure of the average region with the models from a single AMP11 simulation, structural similarity was analyzed. As a consequence of the analysis, it was determined that the structural similarity was not stable, despite being nearly concordant (Figure 21A). The stability of the reverse AMP11 chimeric peptide was not the same as that of the straight chimeric peptide (Figure 21B). When the secondary structure of the average region and the secondary structure from a single AMP11 simulation were aligned, it was discovered that the structures were similar, but unstable.

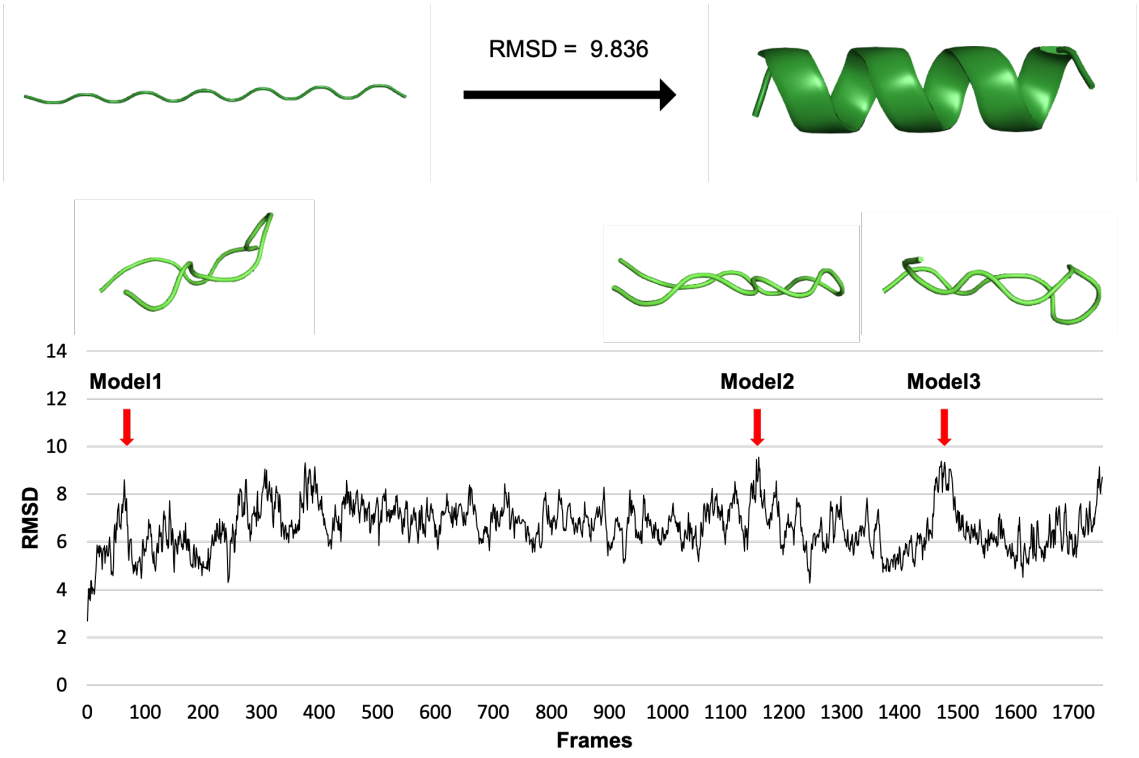

Figure 20. AMP11 Molecular Dynamics Simulation at 35ns to Identify Reference Models for AMP11 Chimeric Peptides Simulation Analysis.

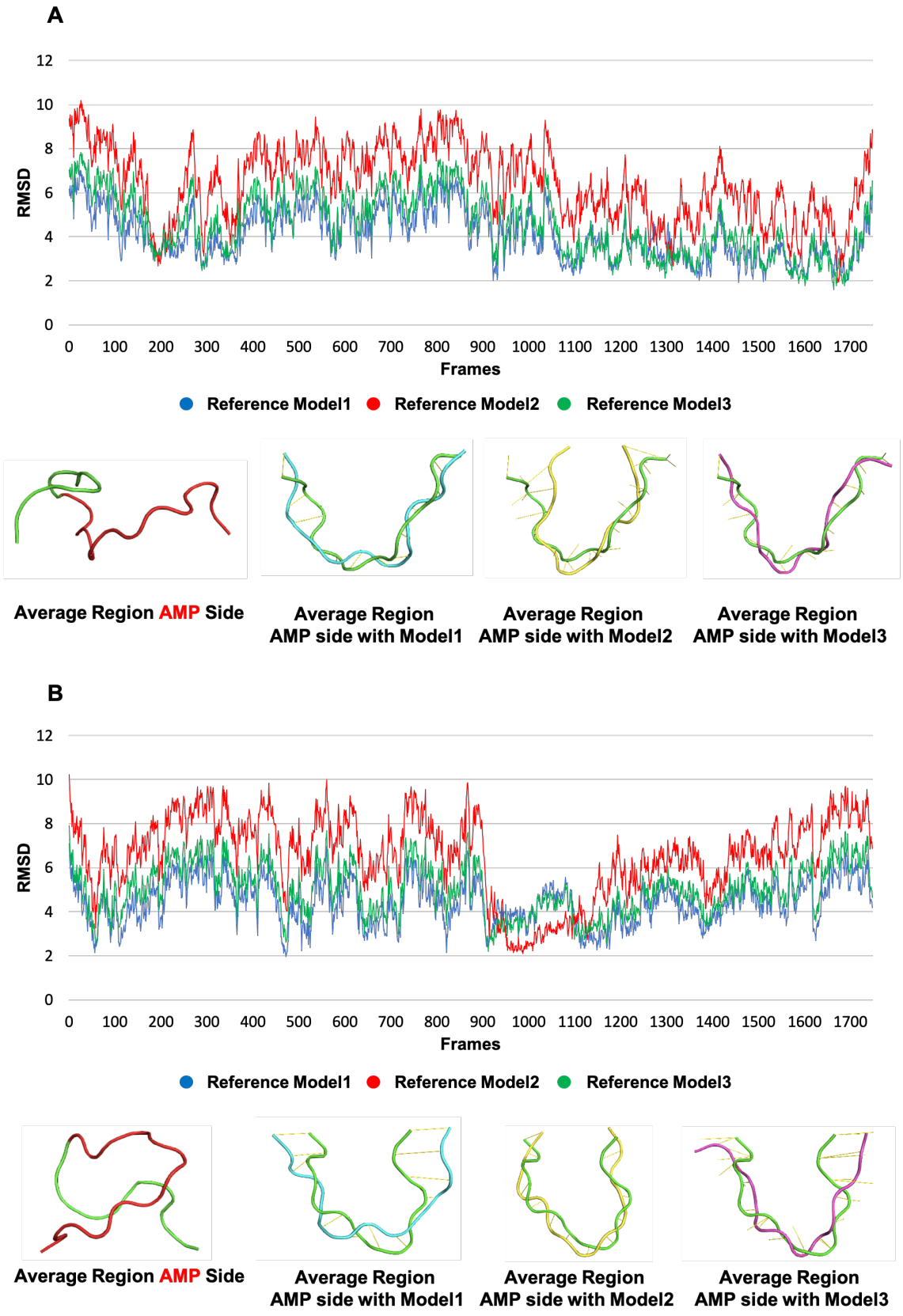

Figure 21. AMP11 Chimeric Peptides Simulation Analysis with Reference Models A) Linear Straight AMP11 Analysis B) Linear Reverse AMP11 Analysis

Consequently, conformational and stability analyses were conducted on all candidate chimeric peptides. Straight AMP1 chimeric peptide showed the greatest results in the analysis. Straight and reverse AMP9 chimeric peptides have good conformation similarity, but their stability is limited. Therefore, these candidates have been determined to be promising candidates. Reverse AMP1, straight AMP11, and reverse AMP11 chimeric peptides failed to demonstrate stability and were therefore ruled out as unsuitable candidates.

CHAPTER 4

CONCLUSION

Implants are considered one of the most effective alternatives for replacing missing teeth. Implants offer benefits such as their mechanical properties, natural appearance, and long-term functionality, which make them highly desirable. However, a significant challenge associated with implants is the colonization of microorganisms on their surfaces, leading to infection issues. This basic problem with implants can be eliminated, making it a much better option. Infection-resistant antimicrobial coatings developed for this have become a promising option. In this study, functional chimeric peptides were designed using antimicrobial peptides and hydroxyapatite binding peptide to provide antimicrobial effect to titanium dental implants with increased biocompatibility by coating with hydroxyapatite. For this purpose, 12 antimicrobial peptides were selected from various databases and literature. Computational secondary structure analysis, solubility analysis and conformational change analysis were performed to analyze whether the designed chimeric peptides could retain their antimicrobial properties.

Antimicrobial peptides appear as thousands of alternatives known to be effective against microorganisms such as viruses, fungi and bacteria in general. However, considering the aim of the thesis, cariogenic peptides effective on microorganisms such as *S. Mutans* and *S. Epidermidis*, which are prominent in implant infection, were investigated. In this context, the peptides were selected considering the strains, low MIC values and sequence length. Peptides with short sequence lengths have come to the prominence due to their low cost and easy synthesis.

In the secondary structure analysis, AMPs and HABP peptides were modeled separately by secondary structure prediction. The PEPFOLD online tool, which is Open Access, was used for the prediction. The reason for using PEPFOLD is that algorithms have been developed focusing on peptides and it gives rapid results. Although there are

many alternative platforms to PEPFOLD, they have not been a proper option due to minimum sequence and maximum sequence restrictions. Secondary structure analysis was performed for AMPs with the result of RMSD by atomic alignment of the AMP side of the chimeric peptide with the single form of AMPs. For the HABP peptide, the HABP side of the chimeric peptide and the RMSD result were analyzed. It is known that for cases where the RMSD score is close to 1, the structural change is less, and the further this score is away from 1, the more the structural change differs. In this context, as a result of the analysis of AMPs, it was observed that the structural change was the least in AMP1, AMP9 and AMP11 chimeric peptides. These chimeric peptides have been identified as promising candidates for further analysis.

As a result of secondary structure analysis, AMP1 AMP9 and AMP11 chimeric peptides were subjected to solubility analysis as promising candidates. The reason for this is that peptides can lose their properties by entering hydrophobic-hydrophobic interactions when they are extremely hydrophobic. In particular, antimicrobial peptides have amphipathic properties and provide their antimicrobial effects depending on this property. The structurally corrected method of CAMSOL, the Open Access tool, was used for solubility analysis. In the structurally corrected method, the ideal diameter value was given for each peptide based on the distance between two alpha C atoms, and the proximity-distance relationship of amino acids and the solubility score for each amino acid were calculated. In order to evaluate the results, a score of 1 and above was associated with hydrophilic, a range of 0 to 1 with hydrophilic affinity, a range of 0 to -1 with hydrophobicity, and a score of -1 or lower with hydrophobicity. In the solubility analysis, the lower limit and ideal range for the appropriate hydrophobicity were determined. In order to do this, solubility analysis of 12 antimicrobial peptide candidates was performed. In the analysis, -3 was determined as the lower limit, while the ideal range was determined as 3 to -3. Subsequently, the analysis of straight and reverse chimeric peptides AMP1, AMP9 and AMP11 was performed. Although the AMP1 chimeric peptide was seen in limit, it was observed that it shifted to hydrophilicity compared to single AMP1. In addition, AMP1 was identified as a promising candidate as it is known to be one of the most effective peptides in the literature. When straight and reverse AMP9 chimeric peptides were analyzed, it was found to be in the ideal range. Finally, analysis of straight and reverse AMP11 chimeric peptides showed that both were in the ideal range, as with

AMP9 chimeric peptides. As a result, all analyzed chimeric peptides were identified as promising candidates as a result of solubility analysis.

Molecular Dynamics simulations were performed to analyze the time-dependent conformational changes of AMP1, AMP9 and AMP11 chimeric peptides from secondary structure analysis and solubility analysis. For this analysis, conventional molecular dynamics simulation was used. As an alternative to conventional MD, accelerated MD or all atom MD simulations can also be performed. For MD simulations, linear secondary structures of single AMP1, AMP9, AMP11 and chimeric candidates were constructed. Afterwards, a waterbox was created using water molecules and ions with the peptides in the center. Here, the addition of ions is to ensure that the medium is neutralized. Finally, simulations of 35 ns were performed. In the simulation of single antimicrobial peptides, the highest points were determined as the reference point for chimeric simulations of the models at that point, assuming the highest conformational change. Then, the distance from the starting point and stability of the lowest points were examined in the chimeric simulation analysis. Stability of approximately 20 ns was seen for the straight AMP1 chimeric peptide. For the reverse AMP1 chimeric peptide, it was observed that it progressed at the starting point, that is, it did not undergo conformational change. Although a stability of about 4 ns was observed for the straight AMP9 peptide, there was a rapid return to the starting point, that is, to the point where there was no conformational change. For reverse AMP9 chimeric peptide result showed almost 12 ns stability and structural similarity by lower scores from starting point. Finally, there was no stability and any structural similarity from starting point to final point for the straight and reverse AMP11 simulation results. As a result of the conformational analysis of chimeric peptide candidates, straight AMP1, straight AMP9 and reverse AMP9 were determined as the best candidates.

In conclusion, the design platform outlined in this work can be expanded further with other antimicrobial peptides. This approach will eliminate the need for the test processes used in determining effective chimeric peptides, thus reducing both time and cost associated with the chimeric peptide determination process. Once fully developed, the chimeric peptide design tool described in this thesis can be employed to rapidly design bifunctional peptides for infection-resistant implant coatings.

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