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Review Article

Periodontal vaccines -past, present and future-A literature review

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ABSTRACT

Edward Jenner introduced vaccination using cowpox virus in the late 18th century. Periodontal diseases, stemming from various microbes, contribute significantly to adult tooth loss. Current treatments only manage disease progression, prompting a need for advanced therapies like vaccines targeting specific periodontal bacteria. Periodontal vaccination shows promise, although no study has met all criteria for an ideal solution. The goal is to identify antigens in periodontitis and stimulate antibody production. Future integration with mechanical therapy aims to reduce the global burden of periodontitis and associated morbidity. This paper explores current and future approaches to periodontal vaccinations.

1. Introduction

A substance derived from naturally dead or weakened pathogens and administered to the body to enhance immunity against or treat a disease is known as a vaccine. The application of immunological principles to human health through vaccination is widely recognized and significant. Vaccines primarily serve as preventive measures, mitigating the severity of subsequent infections. In this review, we will discuss three types of vaccinations:[1]

Periodontitis, a condition affecting the tissues supporting tooth structure, stands as one of the most prevalent oral diseases. Its causes encompass both local factors within the oral cavity and systemic influences, impacting not only dental health but also the overall well-being of patients.[2]

In the current understanding of periodontal disease, the interplay between the host and microbial agents plays a pivotal role in determining the extent and severity of tissue damage. While periodontal pathogens initiate the disease process, the progression and outcome are heavily influenced by the host's immune response. Periodontal diseases manifest as inflammatory reactions triggered by microbial plaque, leading to degradation of tissues, bone loss, and ultimately, tooth loss when occurring in a susceptible periodontium.

Periodontal pathogens, such as Porphyromonas gingivalis, Tannerella forsythia, and Aggregatibacter actinomycetemcomitans, are Gram-negative anaerobic bacteria that play a significant role in the development and progression of periodontal disease. These bacteria produce various antigens that can trigger an immune response in the host.

When these pathogens invade the periodontal tissues, they interact with the host's immune system, leading to the activation of pro-inflammatory cells. These activated cells release a multitude of cytokines, which are signaling molecules that regulate immune responses.

Some antigens produced by periodontal pathogens can stimulate different types of helper T cells, specifically Th1 and Th2 cells. Dendritic cells, specialized antigen-presenting cells, capture these antigens and present them alongside major histocompatibility complex (MHC) antigens to CD-8 or CD-4 cells.

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Table 1: Three types of vaccinations:

Type of Vaccination	Description
Active Immunization	Active immunization involves stimulating a person's immune system by administering killed or live, attenuated products made from microorganisms. This method prompts the body to produce its own antibodies and develop immunity against the targeted pathogen. Examples include vaccines against diseases like measles, mumps, rubella, and influenza.
Passive Immunization	Passive immunization entails the transfer of pre-formed antibodies from one individual to another. Instead of inducing the recipient's immune system to produce its own antibodies, passive immunization provides immediate protection against specific pathogens. This approach is typically used for individuals who require rapid immunity or those unable to mount an effective immune response. Examples include the administration of antibody-rich preparations such as immune globulins or monoclonal antibodies.
DNA Immunization	DNA immunization involves the administration of DNA plasmids containing genes necessary for producing antigens. Rather than delivering antigens directly, this method prompts the recipient's cells to produce antigenic proteins, triggering an immune response. DNA vaccines offer potential advantages such as ease of production, stability, and the ability to induce both humoral and cellular immune responses. They are under investigation for various infectious diseases and cancers.

Table 2: Vaccination milestones[3]

Milestone	Description
Cowpox Vaccine (Late 18th Century)	Edward Jenner introduced the cowpox vaccine, marking the world's first vaccine. By utilizing the cross-protection provided by the cowpox virus, Jenner established the concept of vaccination, demonstrating protection against smallpox. This groundbreaking achievement laid the foundation for modern vaccination practices.
First Anti-Rabies Vaccine (1885)	Louis Pasteur developed the first anti-rabies vaccine in 1885. This vaccine marked a significant advancement in vaccine development, providing protection against rabies, a deadly viral infection transmitted through animal bites. Pasteur's work laid the groundwork for future advancements in immunization and contributed to the control of rabies worldwide.
Identification of Immunological Memory (20th Century)	Despite early vaccine development, the understanding of immunological memory and the role of lymphocytes remained limited until the 20th century. French microbiologist Louis Pasteur, the pioneer of vaccination, did not fully comprehend these concepts in his time. It wasn't until later discoveries, such as Burnet's clonal selection theory (1957) and the identification of T and B lymphocytes (1965), that the main mechanisms underlying vaccination were elucidated.

Table 3: Host immune relationship[3]

Category	Chemicals
Virulence Factors for Microorganisms	- Lipopolysaccharides
	- Bacterial enzymes
	- Toxic compounds
	- Microbial invasion techniques
	- Fimbriae
	- Bacterial deoxyribonucleic acid (DNA)
	- Extracellular deoxyribonucleic acid (DNA)
Host Inflammatory Response	- Matrix metalloproteinases (MMPs)
	- Prostaglandins
	- Cytokines

When CD-8 cells are activated, they trigger a Th1 response. This Th1 response is characterized by cell-mediated immunity, where immune cells directly target and destroy infected cells. Additionally, Th1 responses lead to the production of pro-inflammatory mediators, such as interferon-gamma and tumor necrosis factor-alpha, which contribute to the inflammatory process in the periodontal tissues.

Conversely, activation of CD-4 cells results in a Th2 response. Th2 responses are associated with antibody production, particularly immunoglobulin G (IgG) antibodies, and the release of protective mediators such as interleukin-4 and interleukin-10. These antibodies and mediators help in combating the infection and resolving inflammation.

Overall, the interaction between periodontal pathogens and the host's immune system leads to a complex interplay of immune responses, involving both Th1-mediated cell-mediated immunity and Th2-mediated antibody-mediated immunity. This immune response determines the outcome of periodontal disease progression and the balance between tissue destruction and repair.[4]

Periodontal vaccines are a potential avenue for preventing or treating periodontal disease by targeting the bacteria responsible for its onset and progression. These vaccines aim to stimulate the host's immune system to recognize and mount an effective response against periodontal pathogens, thus preventing their colonization and reducing inflammation in the periodontal tissues. There

Table 4: Major periodontopathogens, their characteristics, and the types of immune responses they elicit:

Periodontopathogen	**Characteristics**	**Immune Response**
Porphyromonas gingivalis	Gram-negative anaerobic bacterium	Pro-inflammatory response; excites Th1 or Th2 cells
Tannerella forsythia	Gram-negative anaerobic bacterium	Pro-inflammatory response; excites Th1 or Th2 cells
Aggregatibacter actinomycetemcomitans	Gram-negative anaerobic bacterium	Pro-inflammatory response; excites Th1 or Th2 cells
Immune Cell Type	**Response**	**Mediators**
CD-8 cells	Th1 response	Cell-mediated immunity
CD-4 cells	Th2 response	Antibody (Ab) response
Type of Periodontal Vaccination	**Description**	
Stock Vaccines	Vaccines prepared from standardized stocks of pathogens or their products, typically administered to a population.	
Autogenous Vaccines	Vaccines derived from an individual's own pathogens, tailored to their specific infection profile.	
Pure Cultures Vaccines	Vaccines containing pure cultures of specific pathogens, such as Streptococcus, aimed at inducing immunity.	

are different types of periodontal vaccines, each with its own mechanism of action and potential impact on overall health:

1. **Subunit Vaccines**: These vaccines contain specific antigens derived from periodontal pathogens, such as Porphyromonas gingivalis, Tannerella forsythia, or Aggregatibacter actinomycetemcomitans. These antigens are selected based on their ability to induce an immune response without causing disease. Subunit vaccines may target surface proteins, virulence factors, or toxins produced by periodontal pathogens. The mechanism of action involves stimulating the production of antibodies and memory T cells that can recognize and neutralize the pathogens upon subsequent exposure.
2. **Live Attenuated Vaccines**: These vaccines contain live but weakened forms of periodontal pathogens. Through a process of attenuation, the pathogens are modified to be less virulent while still retaining their antigenic properties. Live attenuated vaccines mimic natural infection, eliciting a strong and long-lasting immune response. However, safety concerns regarding reversion to virulence or potential adverse effects limit their development.
3. **DNA Vaccines**: DNA vaccines utilize plasmid DNA encoding antigens from periodontal pathogens. When administered, the DNA is taken up by host cells, leading to the expression of the encoded antigens. This triggers both innate and adaptive immune responses, including the production of antibodies and cytotoxic T cells. DNA vaccines offer the advantage of easy production and storage but may require adjuvants or delivery systems to enhance their immunogenicity.
4. **Vector Vaccines**: Vector vaccines employ attenuated viruses or bacteria as delivery systems to introduce antigens from periodontal pathogens into the host. The vector acts as a carrier, delivering the antigens to immune cells and triggering an immune response. Viral vectors, such as adenovirus or adeno-associated virus, and bacterial vectors, such as attenuated strains of Salmonella or Lactococcus, have been investigated for their potential in periodontal vaccine development.

The impact of periodontal vaccines on overall health extends beyond oral health. By preventing or reducing periodontal disease, these vaccines may contribute to the mitigation of systemic inflammation and the associated risk of various systemic conditions linked to periodontitis, including cardiovascular disease, diabetes, and adverse pregnancy outcomes. Additionally, improved oral health can enhance quality of life by reducing pain, tooth loss, and the need for invasive dental procedures. However, further research is needed to optimize vaccine formulations, delivery methods, and efficacy, as well as to assess long-term safety and immunological memory.[5]

2. Materials and Methods

To conduct a comprehensive review on the topic of periodontal vaccines, the following steps were undertaken:

1. **Initial Search on Google Scholar**: A preliminary search was performed on Google Scholar to gather a sample of relevant articles. Keywords such as "periodontal vaccines," "periodontal disease prevention," and "periodontal immunization" were used to identify initial literature.
2. **Subsequent Search on Databases**: Following the initial search, more focused searches were conducted on databases such as Science Direct, ADA (American Dental Association), FDI (Fédération Dentaire Internationale), and PubMed. These searches were refined to include articles published up to March 2024, ensuring the inclusion of the most recent literature on the topic.
3. **Identification of Peer-Reviewed Articles**: Nine peer-reviewed articles were identified through the

Table 5: Types, need, Mechanism of action & impact over overa all health of periodontal vaccines[5]

Type of Vaccine	Need	Mechanism of Action	Impact on Overall Health
Subunit Vaccines	Addresses specific antigens associated with periodontal pathogens.	Stimulate the immune system to produce antibodies against specific components of periodontal pathogens, preventing their attachment and invasion into periodontal tissues.	Generally safe, as they contain only the antigens necessary to trigger an immune response. May lead to enhanced immune function and reduced risk of periodontal disease, indirectly benefiting overall health.
DNA Vaccines	Addresses specific genetic material from periodontal pathogens.	Introduce DNA sequences encoding antigenic proteins into host cells, triggering the production of antigenic proteins by the host, which in turn stimulates an immune response.	Generally safe, with low risk of adverse reactions. May enhance immune response and contribute to overall health by preventing periodontal disease progression.
Live Attenuated Vaccines	Addresses weakened forms of periodontal pathogens.	Introduce weakened, but still viable, forms of periodontal pathogens to the host, stimulating a robust immune response without causing disease.	May provide long-lasting immunity, but can pose a risk to individuals with compromised immune systems. Impact on overall health depends on the specific pathogen and individual health status.
Killed or Inactivated Vaccines	Addresses inactivated forms of periodontal pathogens.	Introduce killed or inactivated forms of periodontal pathogens to the host, stimulating an immune response without causing disease.	Generally safe, with low risk of causing disease. May provide protection against periodontal pathogens, indirectly benefiting overall health by reducing the risk of periodontal disease-related complications.
Recombinant Vector Vaccines	Addresses genetically engineered vectors carrying antigenic material from periodontal pathogens.	Use genetically modified viruses or bacteria as vectors to deliver antigenic material from periodontal pathogens into host cells, stimulating an immune response.	Generally safe, although there may be concerns about the safety of the viral or bacterial vectors used. Impact on overall health depends on the specific vector and antigenic material used.

database searches. These articles were selected based on their relevance to the topic of periodontal vaccines and their publication in reputable scientific journals.

4. **Utilization of Professional Sources**: In addition to peer-reviewed articles, insights from professional sources published on reputable websites and journals were accessed. This involved utilizing the internet to supplement information retrieval, ensuring a comprehensive understanding of the topic.
5. **Citation of Sources**: All sources utilized in the review were appropriately cited in the references section of the paper. This included peer-reviewed articles, professional sources, and any other relevant literature consulted during the research process.

By following these steps, a thorough review of the literature on periodontal vaccines was conducted, incorporating both peer-reviewed research and insights from professional sources to provide a comprehensive understanding of the topic.

"Plantibodies"[1–14]

Represent a novel approach in periodontal vaccination, utilizing plants as bioreactors to produce antibodies against periodontal pathogens. This innovative strategy harnesses the genetic engineering capabilities of plants to express and synthesize specific antibodies, thereby offering a sustainable and cost-effective alternative to traditional antibody production methods.

The concept of plantibodies involves introducing genes encoding for the desired antibodies into plant cells, typically via genetic modification techniques. Once integrated into the plant genome, these genes instruct the plant cells to produce and accumulate the antibodies within their tissues. Plants such as tobacco, potatoes, and tomatoes have been explored as potential hosts for producing plantibodies due to their ability to efficiently produce and accumulate foreign proteins.

One of the key advantages of plantibodies is their scalability and ease of production. Unlike conventional antibody production methods, which often require complex bioreactor systems and specialized facilities, plantibodies can be grown and harvested on a large scale in agricultural settings. This scalability makes plantibodies particularly attractive for widespread distribution and mass vaccination campaigns.

Moreover, plantibodies offer the potential for oral administration, eliminating the need for injections and simplifying vaccine delivery. This route of administration leverages the natural mucosal immune response in the oral cavity, potentially enhancing vaccine efficacy and promoting patient compliance.

However, challenges remain in optimizing the expression levels and stability of plantibodies, as well as ensuring

proper folding and post-translational modifications to maintain antibody functionality. Additionally, regulatory considerations surrounding the safety and approval of plantibody-based vaccines need to be addressed.

Overall, plantibodies represent a promising avenue for the development of novel periodontal vaccines, offering the potential for cost-effective production, scalable manufacturing, and convenient administration. Continued research and development in this area hold the promise of advancing the field of periodontal vaccination and improving oral health outcomes.

Table 6:

Limitations of Periodontal Vaccines	Periodontal disease is complex and multifactorial, making it challenging to develop vaccines that target all contributing factors.
	Sustaining sufficient antibody levels over an extended time poses a challenge, potentially requiring booster doses to maintain efficacy.
	Contamination of vaccines is possible during production or storage compromising their safety and effectiveness.
	Toxic responses to fully inactivated vaccinations may occur, necessitating careful monitoring of adverse reaction.
Future of Future of Vaccines	Human trials of the conductrd in vitro studies present a challenge, requiring rigorous clinical evaluation to assess safety and efficacy.
	A pan-gene approach is needed, focusing on multiple representatives of genes involved in periodontal pathogens, rather than targeting one at a time.
	Research and development efforts should aim to involve all pathogens associated with periodontal disease, rather than focusing on individual strains.

3. Discussion

Periodontal disease is a multifactorial condition characterized by inflammation and destruction of the supporting structures of the teeth, including the gums, periodontal ligament, and alveolar bone. One of the primary challenges in developing vaccines against periodontal disease stems from its intricate nature, which involves a diverse range of pathogenic microorganisms.[8]

Periodontal disease is not caused by a single pathogen but rather by a complex microbial community consisting of numerous species of bacteria, fungi, and viruses. Among these, Gram-negative anaerobic bacteria are particularly implicated in the initiation and progression of periodontitis. Species such as Porphyromonas gingivalis, Tannerella forsythia, and Aggregatibacter actinomycetemcomitans are considered major periodontal pathogens due to their ability to induce inflammation and tissue destruction.[8,9]

The presence of this diverse array of bacteria complicates the process of identifying and targeting antigens for vaccination. Unlike some infectious diseases caused by a single pathogen with well-defined antigens, periodontal disease involves multiple species with varying virulence factors and antigenic profiles. Additionally, the microbial composition of the subgingival biofilm can vary among individuals and throughout the course of the disease, further adding to the complexity of vaccine development.[8]

Furthermore, the dynamic nature of the host-microbiota interaction in the periodontal environment presents another challenge. The immune response to periodontal pathogens involves a delicate balance between protective immunity and harmful inflammation. Vaccines must elicit an immune response capable of effectively clearing pathogens while avoiding excessive tissue damage and inflammation. Achieving this balance requires a thorough understanding of the host immune response to periodontal pathogens and careful selection of vaccine antigens and adjuvants.[9,10]

Despite these challenges, research into periodontal vaccines continues to advance. Efforts are underway to identify conserved antigens shared among periodontal pathogens or virulence factors essential for their survival. Novel vaccine delivery systems, such as nanoparticles or mucosal vaccines, are also being explored to enhance the immunogenicity and efficacy of periodontal vaccines.[9]

In conclusion, the intricate nature of periodontal disease, characterized by a diverse range of pathogenic microorganisms and dynamic host-microbiota interactions, presents significant challenges in the development of vaccines. Overcoming these challenges will require innovative approaches and a comprehensive understanding of the complex mechanisms underlying periodontal pathogenesis and host immune response. However, the development of effective periodontal vaccines holds the potential to significantly reduce the burden of periodontal disease and improve oral health outcomes.[10]

Additionally, the possibility of cross-reaction between bacterial antigens and human counterparts further complicates vaccine development. Vaccines containing bacterial whole cells or crude extract preparations may inadvertently trigger immune responses against human tissues, leading to undesirable effects. Moreover, there is a risk of vaccines inadvertently containing harmful proteins, toxins, or live viruses, which could pose significant risks, especially for individuals with hypersensitivities or compromised immune systems.[10–14]

Safety and efficacy concerns also arise with vaccines. While attenuated vaccines are weakened, there is a risk of them reverting to their virulent form, potentially leading to disease transmission. Similarly, supposedly inactivated vaccines may not be completely neutralized, posing potential adverse effects, particularly in immunocompromised individuals.

One major limitation is the interspecies variation in immune system components and responses. The immune system of rodents or non-human primates may not fully mimic the complexity and diversity of the human immune system. This can impact the interpretation of vaccine-induced immune responses and the extrapolation of findings to human populations.

Furthermore, differences in periodontal disease pathogenesis and progression between animal models and humans may affect the relevance of vaccine efficacy assessments. Animal models of periodontal disease often rely on experimental induction methods, such as ligature placement or bacterial inoculation, which may not fully replicate the natural disease process observed in humans. Additionally, the composition of the oral microbiota and host genetic factors influencing disease susceptibility may vary between species, further complicating the translation of preclinical findings to human clinical trials.

Given these limitations, rigorous testing and validation through human trials are essential to ensure the safety and efficacy of periodontal vaccines. Human clinical trials provide critical data on vaccine immunogenicity, safety profiles, and protective efficacy in the target population. These trials involve careful monitoring of vaccine-induced immune responses, potential adverse effects, and long-term outcomes related to periodontal health.

Moreover, human trials allow for the evaluation of vaccine effectiveness in diverse patient populations with varying disease severities, genetic backgrounds, and environmental exposures. This ensures the generalizability of vaccine findings and informs recommendations for broader public health implementation.In conclusion, while animal models play a valuable role in preclinical vaccine development, their limitations in mimicking human immune responses and disease pathogenesis underscore the critical importance of human trials in validating the safety and efficacy of periodontal vaccines. Rigorous testing and validation through human trials are essential steps in translating preclinical findings into clinically effective interventions for the prevention and management of periodontal disease.[15]

4. Conclusion

While current periodontitis treatment methods have limitations, vaccination holds promise as a supplementary therapy to better manage and prevent the disease. Continued research and a holistic approach to vaccine development are necessary to realize the potential of vaccination in improving periodontal health and enhancing the overall well-being of patients affected by periodontal disease.

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6. Conflict of Interest

None.

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