Plant Derived Vaccines – New Door to Periodontal Vaccine

Dr. Devi Bala.R.T1*, Dr. Anupama Tadepalli2

1Post graduate, Department of Periodontics, SRM Dental college, Ramapuram. Chennai -89.
2Reader, Department of Periodontics, SRM Dental college, Ramapuram. Chennai -89

Abstract:
Periodontitis is an immuno-inflammatory disease with multifactorial origin and have high association with systemic disorders such as cardiovascular disease, diabetes mellitus. The widespread nature of the periodontal disease initiated the need for its control and prevention. Plant-based vaccine is an emerging concept in field of vaccination. PubMed, Embase, Web of science, Cochrane, Medline and Google Scholar search engines were used to obtain relevant publications in medical and dental research and appropriate papers were reviewed and findings were briefly summarized. Preliminary studies in the field of medicine and veterinary sciences showed beneficial effect of these plant derived vaccines in a wide array of diseases. This comprehensive review enlightens their scope of application in periodontal therapy.

Key words: Periodontal disease, Plant derived vaccines, Plantibodies, Prevention.

INTRODUCTION:
In general vaccines following active immunization concept, involve stimulation of the antibody production in host by injecting attenuated whole bacterial cell, sub-unit vaccines and synthetic peptides and there by providing immune protection against diseases.[1] Genetic immunization or DNA vaccination are novel techniques in this domain, where genetically engineered DNA is used to elicit host response, eg: plasmid vaccines and live, viral or vector vaccines. [2] Traditionally, passive immunization is a process of supplementation of immunoglobulins such as monoclonal antibodies, to “at risk” individuals to interfere with microbial pathogenesis. [3] Plant based vaccines are an evolving thought of immunization, where plants are infected with genetically engineered DNA to express specific antigens or antibodies. In medicine, the use of transgenic plants for the expression of molecules with diagnostic and therapeutic applications has been very well documented during the last 20 years. In periodontics, they are still an emerging concept of vaccine preparation. This review narrates the scope of plant-based vaccines in periodontal therapy.

PLANT DERIVED VACCINES:
Plant based vaccines involve application of molecular biologic techniques to create transgenic plants which will be used to produce antigens or antibodies. In transgenic plants the DNA is modified by artificial insertion of desired genes using genetic engineering techniques. The inserted gene sequence is known as TRANS GENE. [4] The transgene can then be expressed in the plants either by a stable transformation system or by transient transformation system, depending on the location where the transgene has been inserted into the cells. [4] The first transgenic plant was reported in the year 1983.

• Stable transformation method:
Stable transformation can be done through nuclear integration. It occurs due to the permanent changes caused in the recipient cell genetics, where the target transgene is integrated into the genome of the host plant cells. Lære et al., 2016 stated that stably transgenic plant cells produce a lower amount of subunit antigen, in the range of 0.01 to 0.30% of total soluble plant protein. [4]

• Transient transformation method:
Transient transformation method involves the production of desired protein (Plantibody) soon after the heterologous gene resides transiently in the host cells. The transgene is not incorporated into the genome of the plant cells. In this method, the regeneration of whole plant is not required and the frequency of its occurrence is higher. Plants use their endomembrane and secretory systems to produce large amounts of clinically viable proteins which can later be purified from plant tissue. The expressed plantibodies can be any kind of antibody molecule, ranging from the smallest antigen-binding domains/fragments to full length or even multimeric antibodies.

ADVANTAGES:
Plant based vaccines are highly stable with higher degree of functionality. Application of plants as transgenes account for a large amount of preparation of pharmaceutical compounds with increased therapeutic value. Plants may not have or produce human pathogens. [5] As a result, the resulting vaccines will not have major safety issues for humans as compared to other vaccines such as heat killed vaccines or whole cell antigen which may transmit the pathogenicity.
DISADVANTAGES: Compared to other vaccines, the foremost disadvantage of plantibodies are, that edible vaccines are very likely to be mistaken with normal fruits, and thus, may be consumed more than formulated. Thus, education regarding the consumption of such products are a necessity to ensure adequate safety. Edible vaccines are flushed through a person's system relatively quickly, in a matter of hours or days, before the host's immune system has adapted to producing antibodies.

SCOPE IN DENTISTRY: The need for dental vaccines becomes vital because of the epidemic nature of these diseases. Further vaccines may be beneficial for individuals at risk of advanced periodontal destruction namely, immunocompromised patients by improving the host resistance. Plant based vaccines i.e Plantibodies opened the new door in the dental vaccination. Very few studies are available regarding the application of plant based vaccines towards dental diseases (table 3).

DENTAL CARIES: At current, two plant based dental caries vaccines were studied, namely CaroRx and Guy’s 13 Plantibody. They were prepared from transgenic tobacco plants and these plantibodies bind specifically to Streptococcus mutans, inhibiting the bacterial adherence to salivary agglutinin. (Robinette et al. 2011)

PERIODONTITIS: The concept of periodontal vaccination was initiated in 1980’s. Among these virulent pathogens, Porphyromonas gingivalis is considered as the key stone pathogen. Hence, mainstream of research in periodontal vaccination was focussed on controlling this candidate pathogen and the various vaccines were developed from the virulence factors of P. gingivalis using outer membrane proteins, gingipains, fimbriae, heat shock proteins, lipopolysaccharides (LPS) as sub-unit vaccines or as a whole cell antigen. Table-2 gives the literature studies towards the available periodontal vaccine from 1980’s till date.

DISCUSSION:
Plants being a bio-factories in the production of recombinant proteins offers an exciting alternative for pharmaceutical production of antibodies in large scale. Transgenic plants that express antigens in their edible tissue might be used as an inexpensive oral vaccine production and delivery system. Thus, immunization might be possible through consumption of an “edible vaccine to provide active immunization (Mason et al.1995).

SCAPE IN MEDICINE: In medicine, these vaccines were explored in numerous conceivable ways and the plant-based vaccines were developed towards Bacteria (New castle diseases)[8], Viruses (Human papilloma virus)[9]. Further, vaccines for malignancies such as ovarian, testicular, colon cancer as well as B-cell lymphoma have been under research[10]. A few of the formulated Plant derived vaccines are listed in table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Plant</th>
<th>Vaccine</th>
</tr>
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<tbody>
<tr>
<td>Zeitlin et al</td>
<td>1998</td>
<td>Soya bean</td>
<td>Herpes simplex virus glycoprotein B</td>
</tr>
<tr>
<td>Kapusta et al</td>
<td>1999</td>
<td>Lupin</td>
<td>Plant derived edible vaccine against Hepatitis B virus</td>
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<td>Francoopi</td>
<td>2002</td>
<td>Tobacco</td>
<td>Plant-derived human papillomavirus 16 E7 on coprotein</td>
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<tr>
<td>Hull et al</td>
<td>2005</td>
<td>Tobacco</td>
<td>Antibodies engineered to bind to Bacillus anthracis</td>
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<td>Bernstein</td>
<td>2005</td>
<td>Tobacco</td>
<td>New castle disease virus (NDV) vaccine</td>
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<tr>
<td>Broadzik</td>
<td>2006</td>
<td>Tobacco</td>
<td>Antibodies against Lewis Y antigen in cancer</td>
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<td>Shaaltiel</td>
<td>2007</td>
<td>Carrot</td>
<td>Production of glucocerebrosidase as enzyme replacement therapy in Gaucher's disease</td>
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<tr>
<td>Lai</td>
<td>2010</td>
<td>Nicotiana benthamiana</td>
<td>Monoclonal antibody produced in plants efficiently treats West Nile virus infection</td>
</tr>
<tr>
<td>Langreth</td>
<td>2014</td>
<td>Tobacco</td>
<td>Ebola Vaccine</td>
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Table 1: Plant derived vaccines in medicine
subgingival area of teeth after periodontal scaling and root may be used as a mouthwash or topically applied into the vaccine development, Plantibodies attracted the focus in of periodontics. In the mission of appropriate periodontal immunization protocol for treating periodontal disease and so far passive immunization is not well explored in the field this era. Further the author suggested that, anti-FimA plantibody interactions with native fimbriae on the bacterial cells. inhibits the biological activities of P. gingivalis through plantibody produced in the rice cell sus pension culture induced periodontal disease. They stated that anti -FimA potential vaccine candidate to control P. gingivalis –

Robinette

Limitations:
Invitro and animal studies showed that plant derived vaccines have appreciable therapeutic value to treat various diseases. However, there are many hurdles in their production i.e., such as selection of appropriate plant, selection of virulent antigen, formulation of therapeutic dosage and manufacturing by fulfilling the Good manufacturing Practices Procedures guidelines by WHO. Though preliminary research is demonstrating their usefulness for active or passive immunization to control and prevent the P. gingivalis -induced periodontal disease. Further studies are needed to determine whether anti -FimA plantibody has any modulatory effect on the host immune response to P.gingivalis in vivo and to define an optimal antigen/antibody ratio for eliciting the beneficial immunomodulatory effect.

1. Studies employing P. gingivalis strains with different types of fimbriae and other virulence factors are also required to investigate the plantibody and its usefulness for active or passive immunization to control and prevent the P. gingivalis-induced periodontal disease.

2. Further studies are needed to determine whether anti-FimA plantibody has any modulatory effect on the host immune response to P.gingivalis in vivo and to define an optimal antigen/antibody ratio for eliciting the beneficial immunomodulatory effect.

3. Since, periodontal disease is a poly microbial disease, production of plant derived vaccines towards multiple pathogens from a single plant variety would help in ease of therapeutic application.

**CONCLUSION:**
Periodontitis is stated as a multi-factorial and poly microbial disease. Hence, improving the host immune system in form of vaccination plays a protective role and

**Table 2: Periodontal vaccines**

**Table 3: Plant derived vaccines in dentistry**

enable host to defend against periodontal pathogens. Utilizing the path of plantibodies in the periodontal vaccine may lighten up the way towards host immune modulation and in therapeutic management of periodontal disease.

Conflicts of interest: Nil
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