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Review Article

Applications of Edible Vaccines in Healthcare : Review

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Abstract

Edible vaccines offer several advantages such as cost-effective, easy-to-administer, easy-to-store, fail-safe and acceptable vaccine delivery system, particularly, in poor developing countries. It introduces selected desired genes into plants and then inducing these modified plants to produce the encoded proteins. Numerous delivery systems are available which are useful for preventing infectious diseases, autoimmune diseases, birth control, cancer therapy, etc. There is growing acceptance of transgenic crops in both industrial and developing countries. Resistance to genetically modified foods may affect the future of edible vaccines. They have passed the major hurdles in the path of an emerging vaccine technology. Various technical obstacles, regulatory and non-scientific challenges, though all seem surmountable, need to be overcome.

Keywords : Edible vaccine, oral immunization, medicinal foods and transgenic plants.

Introduction

Vaccines have been innovatory for the anticipation of various infectious ailments. In spite of global immunization of children against the six overwhelming diseases, 20% of infants are still left un-immunized; responsible for approximately two million redundant casualties every year, chiefly in the remote and impecunious parts of the world (Langridge, 2000).

This is due to the limitations on vaccine production, distribution and delivery. One hundred percent coverage is enviable, because un-immunized populations in remote areas can spread infections and epidemics in the immunized safe areas, which have comparatively low herd immunity. Immunization by DNA vaccines is a substitute but this is a costly approach with poor Immune response (Ramsay *et al.,* 1999). Hence, it necessitates for searching cost-effective, easy-to-administer, easy-to-store, safe and socio-culturally readily acceptable vaccines and their delivery systems. Hippocrates stated "Let thy food be thy medicine". Scientists have suggested that genetically modified plants and plant viruses can produce vaccines against diseases such as dental caries; and life-threatening infections like diarrhea, AIDS, etc (Webster *et al.,* 2002). The present article discuss issues related to their commercial development of edible vaccine and their applications in preventing infectious diseases in developing countries.

1. Limitations of conventional vaccines

Conventional subunit vaccines are expensive and technology-intensive, need purifi-

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cation, require refrigeration and produce poor mucosal response (Lal *et al.,* 2007).

2. Advantages of edible vaccines

Edible vaccines have exhibited various fascinating advantages which are given as:

i. Edible vaccines have exhibited efficient mode of action for immunization, however, they do not require subsidiary elements to enhance the immune response.

ii. Edible vaccine unlike traditional vaccines brings forth mucosal immunity.

iii. Edible vaccines are comparatively inexpensive and do not require cold chain storage like conventional vaccines (Nochi *et al.,* 2007).

iv. Edible vaccines have offered better storage opportunities as seeds of transgenic plants contain lesser moisture content and can be easily dried. In addition, plants with oil or their aqueous extracts possess more storage opportunities (Pascual, 2007).

v. Edible vaccines do not require complicated equipments and machines because they could be easily grown on rich soils and the method is economical compared to cell culture grown in fermenters.

vi. Edible vaccines are widely accepted as they are orally administered unlike traditional vaccines that are injectable. Thus, they eliminate the requirement of trained medical personnel and the risk of contamination is reduced as they do not need premises and manufacturing area to be sterilized (Streatfield *et al.,* 2001).

vii. Edible vaccines have offered better opportunity for second-generation vaccines by incorporating various antigens to approach M cells simultaneously

viii. Edible vaccines are safe as they do not contain heat-killed pathogens and hence do not present any risk of proteins to reform into infectious organism.

ix. Edible vaccine production process can be scaled up rapidly by breeding.

3. Preparation of edible vaccines

The desired segment of DNA obtained from the microbes encoding specific antigen can be handled in two different ways:

i. Particular plant virus is genetically engineered to produce the peptides/proteins of interest. The genetically engineered virus is then integrated into the plant to produce a large number of new plants from which chimeric virions are isolated and purified. The resulting edible plant vaccine can be employed for immunological applications.

ii. In another method, the desirable gene is integrated by plant vector via transformation process. Many other approaches have been utilized which can be categorized into following groups:

4.1. *Agrobacterium* mediated gene transfer

In this approach the gene of interest (recombinant DNA) is incorporated into the T-region of a disarmed Ti plasmid of Agrobacterium; a plant pathogen, which is co-cultured with the plant cells, or tissues that needs to be transformed (Fig.-1). This approach is slow with lower yield however; it showed better results in dicotelydenous plants such as potato, tomato and tobacco. Researches in some fields have proved this approach improved in expressing the desirable traits by selected genes in several experimental animals and plants (Mercenier *et al.,* 2001 and Chikwamba *et al.,* 2002).

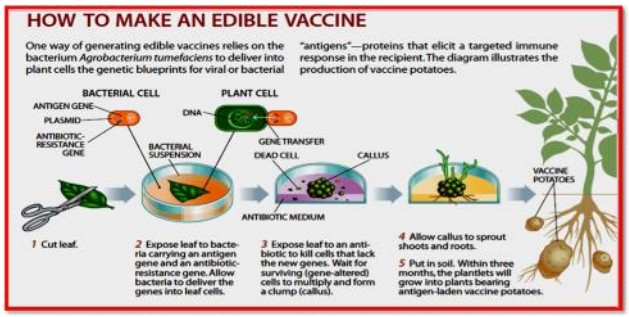

Fig.-1 Process of formation of edible vaccine (Source: Lal *et al.,* 2016)

4.2. Mechanism of Action

Almost all human pathogens attack at mucosal surfaces by urogenital, respiratory and gastrointestinal tracts as their leading path of entry into the body. Thus, chief and prime line of the defense mechanism is mucosal immunity (Arakawa *et al.,* 1998). The most effective path of mucosal immunization is oral route as oral vaccines can produce mucosal immunity, anti-body mediated immune response as well as cell mediated immune response. As an advantage, orally administered antigen containing plant vaccine do not get hydrolysed by gastric enzymes because of rigid outer cell wall of the plant cell. Transgenic plants containing antigens act by the process of bioencapsulation i.e., outer rigid cell wall and are finally hydrolysed and released in the intestines. The released antigens are taken up by M cells in the intestinal lining that are placed on Payer's patches and gut-associated lymphoid tissue (GALT). These are further passed on to macrophages and local lymphocyte populations, producing serum IgG, IgE responses, local IgA response and memory cells, that rapidly counter-balance the attack by the real infectious agent (Lal *et al.,* 2016) (Fig.-2).

4.3. "Second-Generation" Edible Vaccines

Successful expression of desired genes in plant cells and/or its edible segment has attracted the interest of researchers to investigate further and expand the possibility of developing plants expressing more than one antigenic protein. Multicomponent vaccines have been produced by crossing two plant lines possessing distinct antigens. Adjuvants may also be co-expressed along with the antigen in the same plant. B subunit of *Vibrio cholerae* toxin (VC-B) tends to associate with copies of itself, forming a doughnut-shaped five-member ring with a hole in the middle. 1 This feature can bring several different antigens to M cells at one time - for example, a trivalent edible vaccine against cholera ETEC (Enterotoxigenic *E. coli*) and rotavirus could successfully elicit significant immune response to all three (Moss *et al.,* 1999). Global alliance for vaccines and immunization (GAVI) accords very high priority to such amalgamation vaccines for developing countries.

4.4. Various Strategies for edible vaccine synthesis

Approaches to mucosal vaccine formulation include (i) gene fusion technology, creating non-toxic derivatives of mucosal adjuvant; (ii) genetically inactivating antigens by deleting an essential gene; (iii) co-expression of antigen and a cytokine, which modulates and controls mucosal immune response; and (iv) genetic material itself, which allows DNA/RNA uptake and its endogenous expression in the host cell. Various mucosal delivery systems include bio- degradable micro- and nanoparticles, liposomes, live bacterial /viral vectors and mucosal adjuvants (Ruf *et al.,* 2001). Strategy combines different routes of administration and vaccine types, especially where multiple antigens or doses are required (Nemchinov *et al.,* 2000). For example, a single parenteral dose of MV-H DNA (measles virus haemagglutinin) followed by multiple oral MV-H boosters could induce greater quantities of MV-neutralizing antibodies than with either vaccine alone (Modelska, 1998).

4.5. Chimeric Viruses

Certain viruses can be redesigned to express fragments of antigenic proteins on their surface, such as CPMV (cowpea mosaic virus), alfalfa mosaic virus, TMV (tobacco mosaic virus), CaMV (cauliflower mosaic virus), potato virus X and tomato bushy stunt virus. Technologies involved are overcoat and epicoat technology

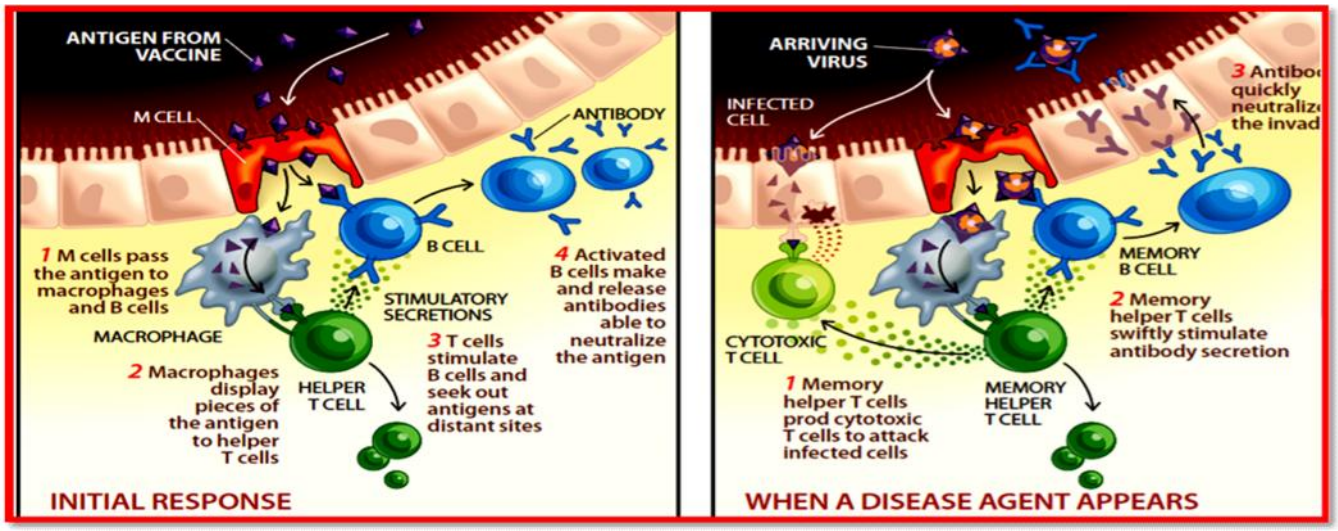

Fig.-2 Mechanism of action of edible action (Source: Langridge, 2000)

(Yusibov *et al.,* 2002). Overcoat technology permits the plant to produce the entire protein, whereas epicoat technology involves expression of only the foreign proteins.

5. Examples of edible vaccines

A number of plants have been used for the production of edible vaccines, some of them are discussed in section given below:

5.1. Transgenic potatoes for diarrhea

The first successful human trial for an edible vaccine was in 1997 to produce transgenic potatoes exhibiting b-subunit of the *E. coli* heat-labile toxin, responsible for diarrhea. Potato-based edible vaccine has a major drawback that it needs to be eaten as raw because cooking causes degradation of protein and makes it poor effective.

5.2. Transgenic tomatoes against diarrhea

Transgenic tomatoes have also been produced at the Cornell University, in the US, against the Norwalk virus, responsible agent for severe diarrhea. The transgenic tomatoes are capable to produce surface protein specific to the virus and it has been shown that mice fed with transgenic tomatoes showed an immune response towards the virus.

5.3. Other transgenic plants

Recently, banana is being widely used as a good source for edible vaccine production because it offers two major advantages (i) it does not require cooking and (ii) locally grown plant. However, the protein expression in transgenic banana is tissue specific promoter dependent. Several other examples involve rabies glyco-protein expressed by viral vectors in spinach (Hafiz and Eyob, 2015) and hepatitis B surface antigen in case of lettuce and potato (Hafiz and Eyob, 2015).

5.4. Applications of edible vaccines in treatment /prevention of diseases

Edible vaccines have contributed a significant role in the diseases prevention, some of the applications are described below:

6.1. Cancer therapy

Several plants have been successfully engineered to produce monoclonal antibodies that have been proved as efficient cancer thera-peutic agents. One example is that of monoclonal body in case of soyabean (BR-96) is an efficient agent that attacks doxorubicin responsible for several types of breast cancer, ovarian cancer,

colon cancer and lung tumors (Hafiz and Eyob, 2015).

6.2. Birth control

Administration of TMV produces protein that is found in *Mousezona pellucida* (ZB3 protein) and is capable of preventing fertilization of eggs in mice due to resulting antibodies (Lal *et al.,* 2016).

6.3. Chloroplast transformation

As the chloroplast genome cannot be transmitted with in crops via usual cross pollination due to its nature of maternal inheritance (Lal *et al.,* 2016). It may contribute to its transmission as well as accumulation in ample quantities in the form of transgenic protein.

6.4. Role in autoimmune diseases

In concern with autoimmune diseases, increasing the self- antigen production in plants is underway in the developmental stage. Few of the diseases that are under investigation are multiple sclerosis, rheumatoid arthritis, lupus and transplant rejection. In one clinical study, strain of mouse vulnerable to diabetes were fed with potatoes capable of producing insulin and a protein called GAD (glutamic acid decarboxylase), associated with CT-B subunit. It has been found that the is therapeutic protein proved successful in suppressing immune attack and delayed the commencement of elevated blood sugar level (Lal *et al.,* 2016).

6.5. Recombinant drugs/proteins

Besides, being major producers of vaccines and antibodies, plant compositions have been modified by engineered viral inoculations to produce enzymes; drugs (albumin, serum protease and interferon) e.g. gluco- cerebrosidase (hGC) production in tobacco plants for treating Gaucher's disease, Interleukin-10 to treat Crohn's disease This method of production is cost-effective. The process of recombinant therapeutic protein production from plants has been commercialized as hirudin which is an anti-thrombin-anti-viral protein that inhibits the HIV virus, trichosanthin (ribosome in activator) and angiotensin-I (antihypersensitive drug) (Lal *et al.,* 2016).

Conclusion

Edible vaccines are effective solution of treatment of some diseases whose control and prevention is limited via traditional vaccines as they have some drawbacks including expensive, storage stability, and expensive logistics. However, some challenges remain, such as the development of edible vaccines using plants whose genetic transformation is difficult to attain or is un-explored, whose cultivars can be developed on all continents with low water and nutritional requirements, and whose consumption may be accomplished in a raw form or with minimal boiling. Advances in the development of transgenic plants and antigen expression for stimulation of the immune system associated with the mucosa have been in the botanical field and not in immunology. Efforts by immunologists and conventional vaccine developers could be of great value to advance this alternative to current vaccines. In addition to their possible benefits, edible vaccines will decrease the costs of vaccination and allow minimally invasive vaccine administration. Furthermore, reiterating the need to increase vaccine performance and stability, developments in the generation of transient vaccines using viruses do not obviate the development of transgenic plants as a long-term and longer-lasting measure. Edible vaccines represent a valuable alternative to mitigate and prevent infectious outbreaks in countries where the conventional vaccination is difficult. In addition, in countries where the prevalence of infectious diseases is controlled, edible vaccines may support public health programs to reduce the risk

of disease outbreaks, analogous to the use of prebiotics and probiotics as a complement to food. However, promoting the genetic transformation of plants with higher impact on the consumption chain in specific countries remains challenging.

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