Plant Based vaccines: New age vaccines for combating pandemics in 21st century

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Abstract -

The phrase edible vaccines (plant based vaccine) was first used by Charles Arntzen in 1990 and refers to any foods; typically plants, that produce vitamins, proteins or other nourishment that act as a vaccine against a certain disease. Edible vaccines or Plant based vaccines offer new potential for reducing the burden of diseases like hepatitis, polio, rota virus and Coronavirus especially in developing countries like Expressing antigens as vaccines and immune modulating antibodies using transgenic plants as bioreactors is a convenient and inexpensive source for production of high-interest immunotherapeutic macromolecules. Toward development of edible vaccines, transgenes of various antigens and antibodies have been expressed successfully in plants, and have been shown to retain their native functionalities. High consideration is being given to addressing technical challenges that can limit expression of immunotherapeutic proteins at sufficient levels in plants. Messenger RNA or mRNA technology, used in Covid-19 vaccines, works by teaching our cells to recognize and protect us against infectious diseases. Production of edible subunit-based recombinant vaccine proteins in the form of leaves, seeds or fruit is expected to be cost effective, and products will be easily stored and transported under limited refrigeration without degradation. Administration of commercial edible vaccines will require significantly less labor and technical training of medical and veterinary personnel. Despite these promising attributes, there still remain concerns and challenges with edible vaccine development, such as achieving maximum expression levels, possible immune tolerance and allergy, as well as environmental contamination concerns.

Keywords - Transgenes, antibodies, antigens, recombinant vaccines, mRNA, Covid-19

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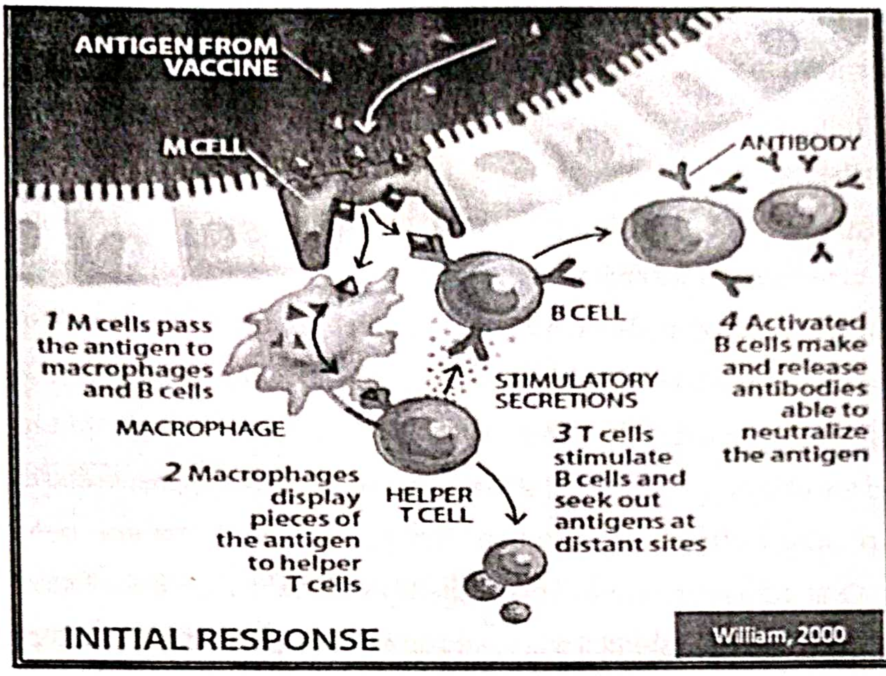
Introduction -

The use of plants as bioreactors for production of recombinant proteins has become well established due in part to specific developments within plant genetics, molecular biology and biotechnology. Introduced as a concept about a decade ago, plant bioreactors are genetically modified (GM) plants whose genomes have been manipulated to incorporate and express gene sequences of useful proteins derived from other biological sources. In this respect, plant-based bioreactor systems offer several advantages over other methods of biological protein production. They are economically grown on agricultural land or in glasshouses and use low-cost inputs such as light, water and minerals. Plant bioreactor systems can be easily adapted to large-scale operations by simply increasing the number of plants. For example, with the current state of technological development, enough hepatitis B antigens to vaccinate all of the approximately 133 million live births in the world each year could be grown on roughly 200 acres of land (Yoshimatsu et al ,2012). Compared with using bacteria or animal cells for production, there is minimal risk of contamination with potential toxins or human pathogens utilizing plant bioreactor systems. Oral ("edible") delivery of subunit vaccine proteins has been shown more efficient compared to subcutaneous or intramuscular injection vaccines due to the increased chance of provoking mucosal immune responses, which in turn stimulate cell mediated responses (Rice et al 2005).



Preparation of edible vaccines

1. Selection of the desired gene and plant

As the first important step, developing edible vaccines involves introduction of selected desired genes into plants and then inducing these altered plants to manufacture the encoded proteins. This process is known as transformation, and the altered plants are called transgenic plants. Toward development of edible vaccine subunit proteins, selection of important epitope region(s) from the pathogen of interest is the one of the key factors that determines the success of potential edible vaccines. A successful edible vaccine should ultimately be safe, non-pathogenic, and able to induce both mucosal and systemic immunity upon entry into the digestive tract. Efficacious edible vaccines should be able to resist the rigid acidic environment of the stomach, and reach the target cells in bioactive form. Selected antigen genes and their required expression machinery should be compatible with the selected plant type. Antigens in transgenic plants are delivered through bioencapsulation within the tough outer wall of plant cells. Bioencapsulation of recombinant antigens with transgenic plant cell vesicles protects the integrity of the antigens from gastric secretions until the plant cell walls degrade in the intestines. Upon degradation, antigens are released, taken up by M cells in the intestinal lining that overlay Peyer's patches and gut-associated lymphoid tissue (GALT). Subsequent antigen processing includes passage to macrophages, other antigen-presenting cells, and local lymphocyte populations. Following vaccination and subsequent exposure to the native pathogen, serum IgG, IgE and local IgA responses, and memory cells are triggered, which would promptly neutralize the attack by the real infectious agent. Like conventional subunit vaccines, edible vaccines are composed of antigenic proteins and are devoid of pathogenic genes. As such, edible vaccines cannot establish infection, which better assures safety, a particularly important consideration for vaccine regimens involving susceptible populations such as immunocompromised patients, children and the elderly. Conventional subunit vaccines can be expensive and technology-intensive, require complex purifi-cation, refrigeration, and produce poor mucosal responses. Oral administration protocols greatly reduce the need for trained medical personnel. Production of potential edible vaccine-quality proteins in transgenic plants is highly efficient and can be readily scaled up for commercial production. Transgenic plants can be engineer-ed to produce immunoprotective proteins against infectious diseases, as well as some autoimmune diseases and human tumors. Transgenic potatoes, tomatoes, maize, rice, and soybeans have been developed and used in various plant bioreactor studies. The results of human trials that have tested several transgenic plant-produced recombinant therapeutic proteins have shown positive responses and no major safety concerns (Yoshimatsu et al ,2012). Transgenic plant-made vaccines are also being used in veterinary medicine. Livestock animals have been fed transgenic plants, including Arabidopsis thaliana, alfalfa and potato, expressing antigens to protect them from various pathogens, including foot-and-mouth disease virus (FMDV), bovine rotavirus (BRV) and bovine viral diarrhea virus (BVDV).

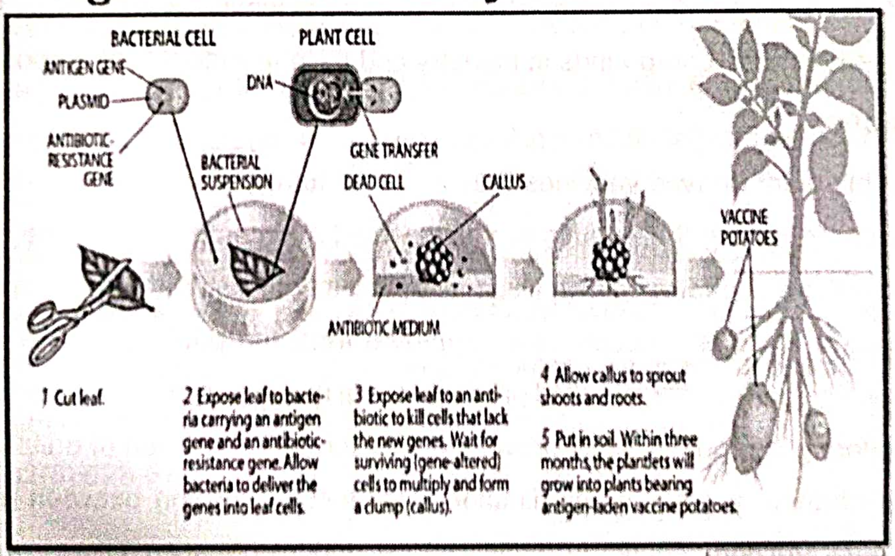
Plants used for edible vaccine

1. Tobacco	7. Soybean
2. Potato	8. Alfalfa
3. Banana	9. Muskmelon
4. Tomato	10. Carrot
5. Rice	11. Peanuts
6. Lettuce	12. Wheat
	13. Corn

2. Vectors with plant-specific super promoters

Edible vaccine development has been challenged by low expression levels of foreign proteins in transgenic plants. Reported expression rates range from 0.01-2% total soluble protein (TSP), which can render edible vaccine proteins less immunogenic. Selection of strong plant-specific super promoters to improve expression levels is another key factor that can determine the success of edible vaccines.

Agrobacterium tumefaciens **method**



William, 2000

3. Plant transformation

The production of transgenic plants is the same as farming regular crops; the differences lie in the transformation process of instilling proteins [Pascual 2007]. There are currently three methods used to produce transgenic plants: 1) gene-gun biolistic particle delivery, 2) Agrobacterium tumefaciens-facilitated transformation, and 3) electropora-tion, with the two most common methods being gene-gun and A. tumefaciens transforma-tion [Streatfield et al, 2006].

4. Transgenic plant screening

Genes for antibiotic and herbicide resistance are used as markers to select for transformed cells and whole plants, which contain the foreign gene(s), and for expressing the desired product, at which time selected (transformed) cells and/or plants can be regenerated (www.plantphys.net).

5. Evaluation of the protein in animal model

Each single antigen expressed in plants must be tested for its proper assembly, which can be verified by animal studies and Western blots, and quantified by enzyme-linked immuno-sorbent assay (ELISA) (Haq et al 1995). Specific protocols for orally administering high-value proteins (e.g. pharmaceutically interesting substances produced in plants) to humans and farm animals requires more scientific study in order to advise the future use of these compounds in industry and for pharmaceutical purposes.

Conclusions

Edible plant-derived vaccines may lead to a future of safer and more effective immunization. Resulting therapeutic products would overcome some of the difficulties associated with traditional vaccines, like costly production, distribution and delivery. The main challenge of edible vaccine is its approval from the public as there are some opinions such as genetically modified products harm the society as well as environment. Close monitoring is required while growing plants for the production of edible vaccines as there is chance of cross-contamination in molecular farming between genetically modified plants and non-genetically modified plants during pollination. There is a possibility of accidental entry of pharmaceutical in to the human food chain and may also affect the wildlife. Edible vaccine can produce complex multimeric proteins that cannot be expressed by microbial system and is a safe and effective method of vaccination. As the benefits of edible vaccines are prominent enough to overcome its side effects, proper research and development in this area is required and it can bring about an era of better control over infectious diseases. The future of vaccines may look more like eating a salad than getting a shot in the arm.

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