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EDIBLE VACCINE: A REVIEW

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ABSTRACT

Edible vaccines represent a useful contribution to the branch of biotechnology as they supply protection against various diseases. Edible vaccines is an application of molecular forming which refers to protein products with clinical or veterinary application produced in recombinant plant system. Edible vaccines are genetically modified crop, in which edible part generally fruit or vegetable act as a vector of vaccine. Edible vaccines hold great vow a cost-effective, easy-to-administer, easy-to-store, fail-safe and sociocultural readily acceptable vaccine delivery system. Vaccines help in stimulating the antibodies production in human and animals and provide immune protection against several diseases. Edible vaccines and biopharmaceuticals have the advantages that there is need for expensive purification system and other expenses associated with cold storage, transportation sterile delivery.

Edible vaccines possess both mucosal and systemic immunity. Numerous delivery systems are available. Which are useful for preventing infectious diseases, autoimmune diseases, birth control, cancer therapy etc. Edible vaccines developed to treat various diseases such as malaria measles hepatitis B , stopping autoimmunity in type-1, diabetes, cholera, enterotoxigenic , Escherichia coli (ETEC), HIV and anthrax..

INTRODUCTION

Edible vaccines are designed to elicit an immune response without causing diseases. The administration of vaccines is cost effective method of combating the spread of diseases. Edible vaccines is elimination of contamination with animal viruses-like cow disease, which is a vulnerability in vaccines developed from cultured mammalian cells, since plant viruses cannot infect humans. Edible vaccines provide protection against various infectious diseases and vaccination is most efficient and cost effective, it is difficult for the people in developing countries to afford it. The main limitation with vaccines is their dependence on cold chain system, which is used to store and transport the vaccines under strict controlled conditions. In the last decade, advancement in the field of medicine and healthcare have been possible because of the development of newer, safer and highly effective vaccines; recombinant vaccines, submit vaccines, peptide vaccines and DNA vaccines to name a few. Although these vaccines have an undue advantage over traditional conventional vaccines, there is a flip side to them.

So, as alternatives had to be thought of, it was envisaged that plants could be used as a cheap, safe and efficient production system for vaccines and thus the concept of edible vaccines was born. The high cost of the traditional biopharmaceuticals is mainly due to the complex production and its cold storage, transportation and delivery needs. A promising alternative is the production of vaccines in plants that could be grown locally, as edible, plant based recombinant vaccines as they are inexpensive, safe, and easy to administer.

Ideal properties of edible vaccine:

- It should not be toxic or pathogenic.
- Low levels of side effect.
- It should not be contaminate the environment
- It should not cause problems in individual.
- Technique of vaccination should be simple.
- It should be cheap.
- It should be effective and affordable.

Type of edible vaccines:

1. Live, attenuated vaccines
2. Inactivated vaccines
3. Subunit vaccines

4. Toxoid vaccines
5. Conjugated vaccines
6. DNA vaccines
7. Recombinant vector vaccines

Live, attenuated vaccines: An attenuated vaccine is vaccine created by reducing the virulence of pathogen, but still keeping it viable. These vaccines contrast to those produced by ‘’killing ‘’ the virus

Inactivated vaccines: An inactivated vaccine is a vaccine consisting of virus particles, bacteria, or other pathogens that have been grown in culture and then lose disease producing capacity. In contract, live vaccines use pathogens that are still alive.

Subunit vaccines: A subunit vaccine is a fragment of pathogens, typically a surface protein, which is used to trigger an immune response and stimulate acquired immunity against the pathogen from which it is derived.

Toxoid vaccine: Toxoid vaccine made from a toxin that has been made harmless but that elicits an immune response against the toxin. Toxoid vaccines are based on the toxin produced by certain bacteria.

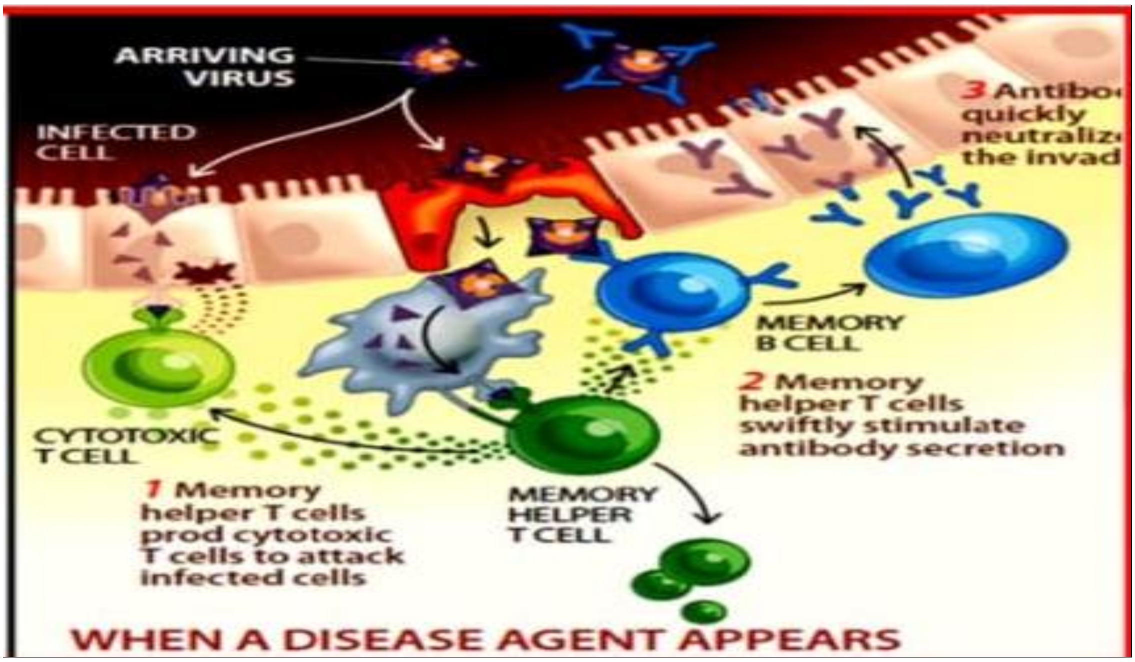
Conjugated vaccine: Conjugated vaccine combines a weak antigen with strong antigen as a carrier so that the immune system has stronger responses to the weak antigen.

DNA vaccines: A DNA vaccine uses a gene from a virus or bacteria to stimulate the immune system. When DNA vaccine is administered to a patient, the machinery in their cells makes a viral or bacterial protein which their immune system recognizes as being foreign to the body.

Recombinant vector vaccine: Recombinant vector vaccines are live, replicating viruses that are engineered to carry extra genes derived from pathogens and these extra genes produce proteins against which we want to generate immunity.

Mechanism of action of edible vaccine:

Almost all the pathogens attack at mucosal surfaces by urogenital, respiratory and gastrointestinal tracts as their leading path of entry into body. Thus, chief and prime line of the defense is mucosal immunity. The main advantage of the edible vaccines is that it protects the antigenic protein from the acidic PH of the stomach and prevents the digestion and the antigen thus ensures the safe and efficient delivery of the antigen to the intestine. The principle of bio encapsulation plays a major role in this, as the though cell walls of the plants help in safe guarding he antigenic protein within it.



Mucosal immunity, the first line of defense mechanism SA against most of the pathogens entering though musoca like mycobacterium tuberculosis and agents causing HIV, diarrhea, pneumonia is being efficiently ensured in the edible vaccines mechanism. Edible vaccines when taken orally undergoes mastication process and the majority of the plant cell degradation occurs in the intestine as a result of action on digestive or bacteria; enzymes on edible vaccines As the principle of bio encapsulation acts upon it and these ensure mucosal immunity, antibody mediated immune response. The antigen which is safely delivered to the intestine is taken up by the payers patch, where the digestion of the plant vaccines and release of the antigens takes place. These antigens are taken up by the M cells and presented to the B cell. The antigen then contact with M cells then contacts with the lumen with broad membrane process and contains a deep investigation in the bastolateral plasma membrane. This pocket is filled with a cluster of B-cells, T-cells and macrophages. M-cells express class II MHC molecules and antigens transported across the mucous membrane by M-cellscan activate B-cells within these lymphoid follicles. The activated B-cells leave the lymphoid follicles and migrate to diffuse mucosal associated lymphoid tissue (MALT) where they differentiate into plasma cells that secrete the IgA class of antibodies. These IgA antibodies are transported across the epithelial cells into secretions of the lumen where they can interact with antigens present in the lumen. The induction of mucosal immunity by edible vaccines is depicted.

Second generation edible vaccines:

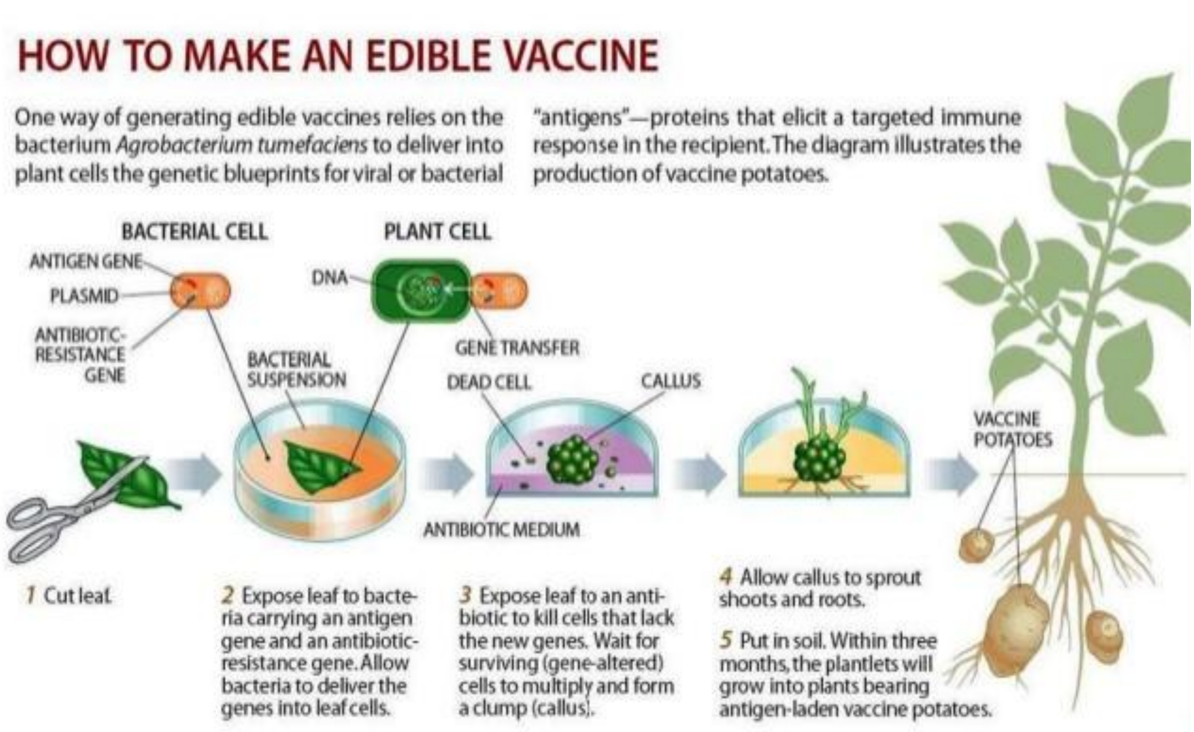
Successful expression of foreign in plant cells and/or its edible portions has given a potential to explore further and expand the possibility plants expressing more than one antigenic protein. Multicomponent vaccines can be obtain by crossing two plant lines harbouring different antigens. Adjutants may also be co-expressed along with the antigens in the same plant .This feature can bring several different antigens to M-cells at one time –for example ,a trivalent edible vaccine against cholera , E.coli and rotavirus could successfully elicit significant. Immune response Global alliance for vaccines and immunization (GAVI) accords very high priority to such combination vaccines for developing countries

Edible vaccines production: The desired segment of DNA obtained from the microbe encoding specific antigen can be handled in two different ways:

1. Particular plant virus is genetically engineered to produce the peptides/protein 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.

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

1. Agrobacterium mediated gene transfer: Agrobacterium is a gram negative pathogenic bacterium involved in causing crown gall formation disease in plant species. The suitable gene of interest is extracted and it is inserted into the T-region of Ti plasmid agrobacterium is allowed to infect the explants by allowing the cultivation. The live bacteria are then killed using the bacteriostatic medium and then transferred to selective medium which favors the transformants and the non transformants are eliminated. The transformants are then cultured on suitable media and then evolved into mature plants though a series of biotechnological techniques.



2. Biolistic method:

Biolistic method is used as a method of transformation of plants, including monocotelydenous plants. The gene containing DNA coated metal (e.g. gold, tungsten) particles are fired at the plant cells using gene gun. Plant cells that can take up the DNA are allowed to grew in new plants and are clones to produce large number of genetically identical crop. This method is more often suitable to deliver DNA into cells of the plant that makes the transfer of genes independent of regeneration ability of the species. The limitation is that the technique is not economical because of particle gun devices.

3. Electroporation method:

In this method, DNA is inserted into the cells after which they are exposed to high voltage electrical pulse which is believed to produce transient pores within the plasma lemma (a thin layer of tissue that covers surfaces). The cell wall acts an efficient barrier to DNA. Hence, it has to be weakened by enzymatic treatment thus permit the entry of DNA into the cell cytoplasm.

4.Chimeric method:

Plants viruses are genetically modified to carry the desired genes and used to infect their natural hosts such as the edible plants where the cloned genes are expressed to varying degrees in different edible part of the plant. Certain viruses can be redesigned to express fragments of antigenic proteins on their surface, such CPMV (Cowpea mosaic virus), alfalfa mosaic virus, TMV (Tobacco mosaic virus), CaMV (Cauliflower mosaic virus), potato virus and tomato bushy stunt virus. Technologies involved are overcoat and epicoat technology. Overcoat technology permits the plant to produce the entire protein, whereas epicoat technology involves expression of only the foreign proteins.

5. Transient method:

In this method of edible vaccines production, the plant viruses are genetically engineered to get a desired protein. These are then allowed to infect the plants and thus within the plants the protein is being produced. This is meant for short term production only as the heritability cannot be assured.

6. Transformation method:

Here the gene of interest from the desired antigen is integrated into the vector and these vectors are then transferred into the plant via Agrobacterium medicated Gene transfer or Biolistic method.

Candidates for edible vaccines:

Edible parts of different species of plants, such as the grains or fruits are utilized for the expression of desired antigen of interest. Cereals like rice and maize fruits like banana, leaves of many plants (Tobacco, alfalfa, peanut leaves), tubers like potatoes, tomatoes, soybean seeds, cowpea, pea, carrot, peanut, and lettuce have been extensively used for high levels of antigenic protein expression. When choosing a plant to be used as a vaccines it is important that it is a palatable with high nutritive and protein content. Plant should be hardly, it should be palatable and well relished, it should be indigenous, easily available and transformation can be done easily.

1. Banana: Banana are sterile so the genes do not pass from one banana to another which is the main reason why bananas are a good choice for the edible vaccine. The typical climate is suitable for growing bananas. Most third- world countries are found in this climates. It does not need cooking. It is inexpensive too and rich source of vitamin A which boosts the immune response.

2. Potato: Potato has served as a vehicle to compound against the diseases like cholera, dengue, and porcine respiratory diseases etc. A potato based vaccines used to combat the Norwalk virus (stomach virus), which is spread by contaminated water and food and causes severe abdominal pain and diarrhea. The main advantages of the potato is affordability by the common and its long shelf life even without refrigeration. The major limitation is it need cooking which can denature antigen and decrease immunogenicity.

3. Tomato: Tomato is one among the widely cultivated vegetables and is quick growing too. Like banana it is also rich in vitamins A which increase immunogenicity. Tomato can be serve as a vector to develop the vaccines against anthrax, rabies and HIV/AIDS.

4. Maize: maize plants generate a protein that is used to develop the hepatitis B virus vaccine. It is cheaper and does not need to be refrigerated.

5. Tobacco:-Tobacco plants are a good model for evaluating recombinant proteins and can be harvested a number of times in a year. Human papilloma viruses (HPV) are the causative agent for cervical cancer and also involved in skins, head and neck tumors.

6. Rice: An edible vaccine using genetically altered rice used in cholera treatment. Cholera vaccine exists but provides short-lived protection and requires refrigeration.

7. Miscellaneous candidates: Some other plants which can also be served for vaccine delivery are lettuce (fast-growing but, spoils readily), soybean (direct consumption, can be harvested a number of time in a year. But spoils readily), and wheat (large number of seeds help an in an increased harvest but need cooking).

Factor affecting efficiency of edible vaccines:

1. The enterotoxin in vibrio cholera, the causative agent of cholera, includes a nontoxic submit B (CTB) that helps the toxin bind to gut cells.

2. CTB is also immunogenic as it stimulates an antibody response in humans and animals.

3. Selection of suitable, easy to grow, store and cost effective plant species.

4. Selection of safe, stable antigen

5. Allergic and toxic tissue.

6. Public perception.

7. Delivery and dosing issue.

8. Vaccine regulatory authority and rules.

Applications of edible vaccine:

1. Malaria: To develop malaria vaccines three antigens were used namely merozoite surface protein (MSP)4, MSP 5 and MSP4/5. When mice were orally immunized with this recombinant antigen and co-administration with CTB as mucosal adjuvant, induced immune response

2. Measles: The vaccine currently in use produces 95% seroconversion in individuals who are over the age of 18 months at the time of vaccination. MV-H antigen was selected and induced in tobacco plant with the help of plasmid vector. It is found that serum antibodies were inducing immune response against antigen.

3. Autoimmune diseases: Investigators have identified several cell proteins that can elicit autoimmunity among the people suffering from TYPE I diabetics. An attempt was made for the development of plant based diabetics vaccines in [potatoes and tobacco containing insulin linked to the innocuous B subunit of the V.

4. Hepatitis B: Investigation of single potato was able to provide the amount of HBs Ag needed for one dose. Immunization is the only known method to prevent the diseases. Tomatoes expressing HBsAg are being grown in guarded greenhouse. It was demonstrated that 30 tomato plants were able to provide enough antigens for 4000 vaccines doses.

5. Cholera: Genetically modified potatoes expressing CTB were found to produce both serum and secretory antibodies when fed into mice. Since people eat only cooked potatoes, the effect of boiling on the properties of CTB expressing in transgenic potatoes was examined. It was evidenced that, over half of the vaccine protein survived in its biologically active form even after boiling for 5 min and it proved that cooking does not always inactivate.

6. HIV: Genetically modified tomatoes were developed by injecting two HIV protein genes along with promoters such as CaMV with needle and the expressed protein was demonstrated by polymerase chain reaction in different parts of the plant.

7. Anthrax: Tobacco leaves bombarded with peg gene (anthrax protective antigen [PA] using a gene gun could express a protein structurally identical to the major protein present in existing vaccine.

8. Norwalk virus: Ninety (90%) out of 20 people when administrated transgenic potato expressing Norwalk virus antigen developed seroconvertion. Genetically engineered bananas and powdered tomatoes expressing Norwalk virus are under development phase to combat Norwalk virus.

9. Cancer therapy: Several plants have been successfully engineered to produce monoclonal antibodies that have been proved as efficient cancer therapeutic agents. One example is that of monoclonal body in case of soyabean (BR-96) is efficient agent that attack doxorubicin responsible for several type of breast cancer, ovarian cancer, colon cancer and lung tumors.

10. Birth control: Administration of TMV produce protein that is found in Mousezonapellucida (zb3 protein and is capable of preventing fertilization off eggs in mice due resulting antibodies..

Regulatory aspects:

It has to be set whether or not EVs would be regulated underneath food, medicine or agricultural product. The main aspects foe safety are plant contamination through cross pollination and of vaccine itself in plant debris spreading dust and other pollutant in surfaces and other pollutant in surfaces and ground waters. The transgenic plants need greenhouse segregation and separate bodies that make sure that such plants are not releasing the antigenic protein in the environment by any means. The cultivation and production of pharmaceutical crops should be limited to control the production facilities like greenhouse, or in plant tissue culture, that prevent the environmental release of biopharmaceuticals. Transgenes may spread by sucking insects, pollen and transfer to soil microbes during plant wounding or breakdown of roots and may pollute surface and ground water. An ethical consideration usually restricts clinical trials from, directly assessing protection in humans.

Some patents of edible vaccines:

1. Prodigene: recombinant antigen production and transfer to plants cells using plasmid vector system; vaccine produced in genetically engineered plants for hepatitis B and transmissible gastroenteritis virus.

2. Ribozymepharm: Nucleic acid vaccine used to treat or prevent viral infection in plants, animal or bacteria.

3. Linda: Multiple sclerosis

4. Rubicon Lab: Retrovirus expressed in animal or plant cell useful as virus and cancer vaccines.

Safety aspects:

1. Contamination though cross pollination
2. Vaccine antigen may affect browsing animals.
3. Vaccine contamination via plant debris spreading on surfaces and ground waters.
4. Affect on humans living in the area drinking vaccine polluted water or breathing vaccine polluted dust.
5. Cultivation and production of pharmaceutical crops should be limited to control the production facilities like greenhouse, or in plant tissue culture, that prevent the environment release of biopharmaceuticals.

Clinical trials:

Antigen expression in plants has been successfully shown in the past, like LT-B (ETEC) in tobacco, and potato, rabies virus-g protein in tomato, HBsAg in tobacco and potato, norwalk virus in tobacco and potato. Ethical considerations usually preclude clinical trials from directly assembling protection, except in few cases. In contrast veterinary researchers can asses immune protection more directly.

Future for edible vaccines:

In simple terms, edible vaccines are created by inserting a specific antigen into a plant. Currently in the clinical trials stages, the edible vaccine for hepatitis B seems well on its way to entering phase V, the consumer market.

Edible vaccine have also have applications for many other diseases and areas of medicine. They are used in veterinary field for protecting livestock against parasite diseases. Edible vaccine presents an innovative, new solution to help countless individuals around the world that cannot receive traditional vaccines for a variety of reasons. Based on the advantages that edible vaccines possess, and the current clinical trials research, edible vaccines demonstrate significant potential to become a widespread diseases prevention method.

Conclusion:

Edible vaccine creating inexpensive vaccines that might be particularly useful in immunizing people in developing countries, where high cost, transformation and the need for certain vaccines to be refrigerated can hamper effective vaccination programs.

Compare to conventional vaccine, fruits derived vaccine is needle free, appealing to children, low cost, can be stored to site of use, safe, and provide mucosal and systemic immunity.

Edible vaccine might be solution to get rid of various ailments as it has more advantages compared to tradition vaccine.

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