



## “Edible Vaccines: A New Approach to Oral Immunization”

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### Introduction:

Edible vaccines are nothing but transgenic plant and animal-based production of or those contain agents that trigger an animal's immune response. In simple, plant or animal-made pharmaceuticals are edible vaccines. In 1989, the effort to produce a plant-based vaccine was formulated by Hiatt and co-workers. National Institute of Allergy and Infectious Diseases approved edible vaccine for its remarkable effect of immunogenicity in 1998. This type of edible vaccines offers a cost-effective, needleless, convenient, safe, easy and a better alternative to vaccine production. There were quite a lot of plant-based vaccines have been developed and most of them are at clinical trial phase. Most of the plant-based vaccines were against viruses and bacteria that infect human, animals as well as poultry which cause fatal illness. So far, there is no edible vaccine that was approved by USFDA because, this type of vaccines were characterised under genetically modified crops.

### Production of Edible Vaccines

Mason and Arntzen (1995) described detailed procedure for the production of plant vaccines. Plant vaccines are produced by molecular farming. It is an advanced biological technique used for the production of pharmaceutically beneficial proteins in plants. Plant vaccine is produced by inserting a microbial gene (encodes the microbial protein) into a plant. Expression of this microbial gene in plant cells will produce the protein that can be purified or consumed along with the plant tissue. Production of plant vaccines are illustrated in Fig.1

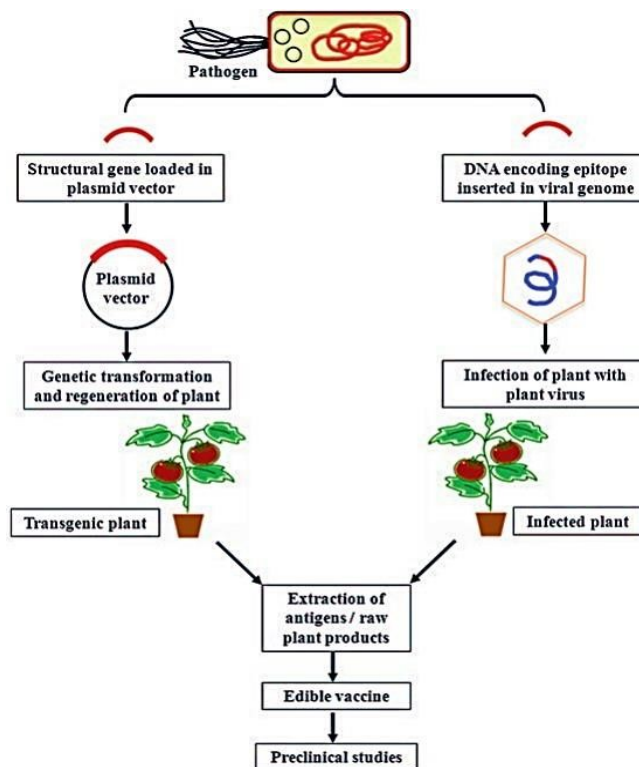


Fig. 1. Production of plant vaccine.

### 1. Plant Transformation

- **Antigenic Gene Transformation through a Suitable Vector**

After transformation of tobacco, great efforts have been made to develop efficient methods for genetic transformation and optimizing expression of foreign genes in plants. The techniques used to introduce foreign genes into plants have been extended to major crops, vegetables, and ornamental and medicinal plants. Various foreign proteins including serum albumin, human  $\alpha$ -interferon, human erythropoietin, and murine IgG and IgA immunoglobulin have been successfully expressed in plants. Humans to prevent possible denaturation during cooking, and avoid cumbersome purification protocols.

#### Ideal properties of Edible Vaccine

- It should be neither toxic nor pathogenic, i.e., it should be safe to administer to human being.
- The vaccination technique should be simple.
- The vaccine should be less cost and should be feasible to consumer.
- It should produce cellular and humoral immunities lasted for long period.
- It should have very low levels or no side effects in normal individuals.
- It should not cause any problems in individuals with impaired immune system. vii. Contamination of the environment should be avoided.

### Mechanism of action of Edible Vaccine

Edible vaccine is a new way of immunization through oral route. This technique will have large contribution to the global vaccine program and might have a dramatic impact on health care sectors in developed and developing countries. Mostly the pathogens attack on mucosal surfaces and therefore, it is the most effective site for vaccination. When these edible vaccines come in contact with the digestive tract lining they activate both systemic and mucosal immunity. This dual effect would offer first-line resistance against pathogens which are entering through mucosa<sup>[15]</sup>. Earlier many researchers have summarized the mechanism of plant vaccines. Mishra and co-workers explained the mode of action in detail. A plant vaccine administered orally stimulates the mucosal and humoral immune system of the host body. Mucosal immune system is the primary defence system and an appropriate site for vaccination. After the administration of plant vaccine, it stimulates the immune system in a systemic manner

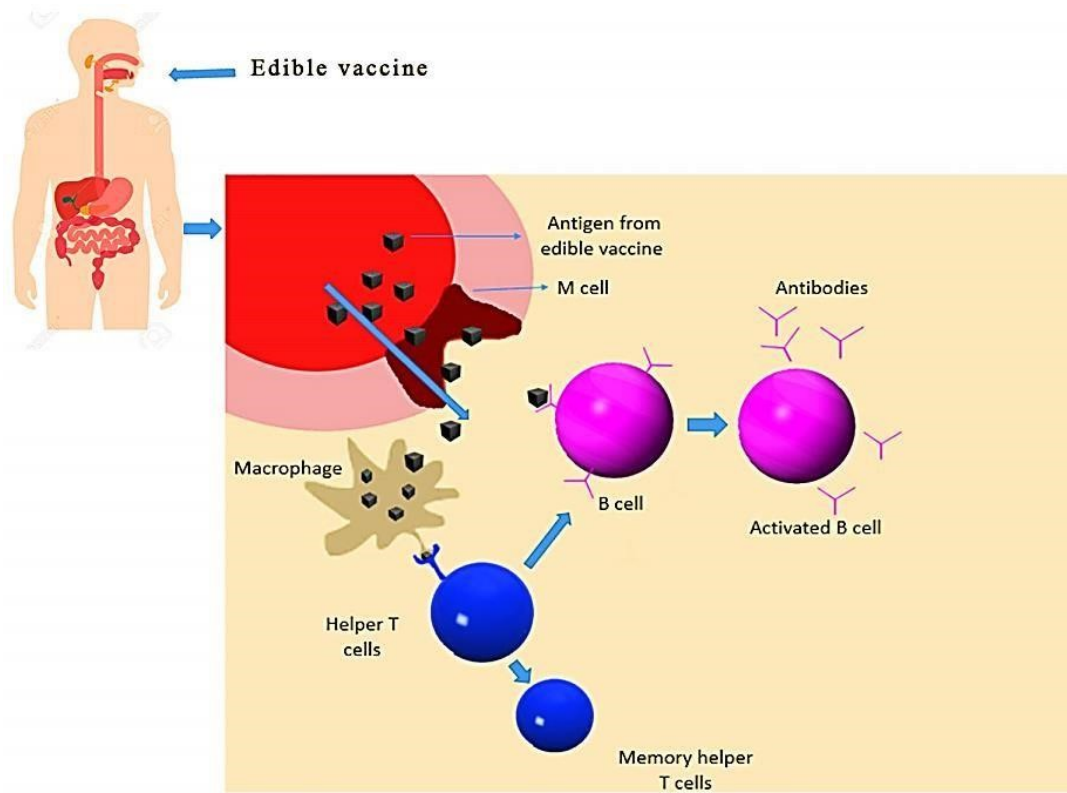


Fig. 3. Mechanism of action of edible vaccines.

## 1. Entry of the Antigen

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### Absorption of Antigen

#### Immune Response

##### *Applications of Edible Vaccine*

##### **Autoimmune disease:**

Scientists have determined that some cell proteins which can induce autoimmunity to the people which are suffering from Type I diabetes maleates. Then there is beginning of development of plantbased vaccines in tobacco and potatoes containing insulin or GAD linked to innocuous B subunits of V. cholera toxin to increase uptake of antigen by M cells.

##### **HIV:**

Initially HIV protein is spliced into CPMV successfully. Then two HIV protein genes and CaMV as a promoter were successfully injected with the help of needle in tomatoes, and these expressed proteins are converted into multiple copies by polymerase chain reaction(PCR) technique in various parts of plants also include the ripe fruits in addition to second generation plant. Recently, for the expression of Tat protein, these proteins are cloned into TMV with the help of inoculation of spinach. Each gram of spinach leaf tissue was containing up to 300-500 µg of Tat antigen. When the mice is fed with this modified spinach followed by DNA vaccination in higher amount antibody than that of control, with the levels peaking at four weeks after vaccination.

##### **Gastrointestinal disorders:**

As per the WHO cholera vaccine can give cross protection against enterotoxin E. coli a heat labile enterotoxin (LT-B). When the transgenic potatoes expressing LT-B were fed to mice, these transgenic potatoes induce production of serum and secretory antibodies. Afterward, evidence also provided that cooking of raw potatoes does not cause inactivation of antigen present in edible vaccine. So, the spectrum of edible vaccines producing plant is expanded beyond the raw food like fruits, flowers, leaves.

##### **Measles:**

Live attenuated vaccine is the only currently available vaccines for measles but they are having certain disadvantages. For preparation of edible vaccine, with the help of plasmid vector MV-H antigen is introduced in tobacco plant. These edible vaccines produce serum antibodies which induce immune response against antigen. The IgA antibodies with antigen also found in the faecal samples of immunized animal.

##### **Malaria:**

Three mainly used antigens are used for the production of malaria vaccine which are Merozoite Surface Protein (MSP) 4, MSP 5, MSP 4/5. This recombinant antigen is orally given to mice along with CBT as mucosal adjuvant, produces immune response. However oral delivery of this malaria vaccine producing immune response is uncertain. Countless efforts and many policies tried to develop a vaccine for malaria.

##### **Norwalk virus:**

When transgenic potatoes expressing Norwalk virus is administered by peoples, there are chances of development of seroconversion in 95% peoples (19 out of 20 peoples). Genetically engineered bananas and powdered tomatoes expressing Norwalk virus are under development phase to combat Norwalk virus.

##### **Regulatory Issues of Edible Vaccine**

It is still unclear whether the edible vaccines would be regulated under food, drugs, or agricultural products and what vaccine component would be licensed—antigen itself, genetically engineered fruit or transgenic seeds. They would be subjected to a very close scrutiny by the regulatory bodies in order to ensure that they never enter the food supply. This would include greenhouse segregation of medicinal plants from food crops to prevent outcrossing and would necessitate separate storage and processing facilities. Although edible vaccines fall under “genetically modified” plants, it is hoped that these vaccines will avoid serious controversy, because they are intended to save lives.

##### **Future Perspectives of Edible Vaccine**

The future of edible vaccine also depends on the WHO standards especially on the safety, purity, effectiveness, cost and with more efficiency. The acceptance and development of transgenic crops at larger scale is also a concern in many developing countries, and if this is accepted by the society then production of edible vaccines and vaccination for the various diseases will be possible worldwide. Presently, microalgae are being used as very valuable and important source which providing active molecules such as chlorophyll, fatty acids, carotenoids, phycobiliproteins and enzymes. Microalgae can be used in future for the recombinant protein expression, pharmaceuticals, immune regulators, hormones, growth factors, nutraceuticals, and many other products such as anticancer agent Taxol and they can be used as edible vaccine. They have many advantages such as formulated at large scale production and fast transformation and fast growth and stable expression level with proper folding and accumulation of multiple antigens as vaccines. They also have effective delivery through oral route. they can be converted into tablets or capsules formulation to ease

the administration and immunogenic response <sup>[11-15]</sup>.

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**CONCLUSION :**

Thirty million children throughout the world do not receive even the most basic immunizations each year. As a result, at least three million of these children die from diseases that are fully vaccine-preventable. The solution to vaccinate these children might seem simple with the idea of large scale production of edible vaccines for various diseases. As a recent progress, the first human clinical trials for plant-based vaccine have been performed; it brings many challenges like optimization of expression levels, stabilization during postharvest storage, etc. Long-term reactions to edible vaccines are yet to be determined. Possible delayed reactions not yet discovered may be the point of consideration. In addition to that, edible vaccines can be further improved for their oral immunogenicity by the use of specific adjuvant which can be applied either as a fusion to the candidate gene or as an independent gene.