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# Candidate Plants: Edible Vaccine

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## Introduction

Vaccines are biological preparations that improve immunity to particular diseases and form an important innovation of $19^{th}$ century research. It contains a protein that resembles a disease-causing microorganism and is often made from weak or killed forms of the microbe. Vaccines are agents that stimulate the body's immune system to recognize the antigen. Now, a new form of vaccine was introduced which will have the power to mask the risk side of conventional vaccines. This type of vaccine was produced from plants which are genetically modified. In the production of edible vaccines, the gene-encoding bacterial or viral disease-causing agent can be incorporated in plants without losing its immunogenic property. The main mechanism of action of edible vaccines is to activate the systemic and mucosal immunity responses against a foreign disease causing organism. An edible vaccine is when the antigen is expressed in the edible part of the plant. This reduces the cost of production of the vaccine because of ease of culturing. In this article, various types of edible vaccines that include algal and probiotics in addition to plants are discussed. Various diseases against which research has been carried out are also reviewed. This article focused on the conception of edible vaccines highlighting the various ways by which vaccines can be delivered.

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 . In 1990, Dr. Arntzen introduced the concept of using transgenic plants to produce and deliver subunit vaccines. This idea of Arntzen proved that the edible vaccine can annihilate the restrictions in the production of traditional vaccines. In tobacco plant, (Streptococcus mutants) a surface antigen is expressed from hepatitis B by Mason et al. is the milestone in edible vaccine production. In parallel to the production of edible vaccine in tobacco, they also started the production of hepatitis B

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and heat-labile toxin B in potato and potato plants. These vaccines have an indefensible advantage of over traditional conventional vaccines. Particularly in the developing world, edible vaccine offer exciting possibilities of reducing the burden of diseases such as hepatitis b and diarrhoea where storing and administering vaccine are often major problems. For production of edible vaccines or antibodies, it is desirable to select suitable plants, algae, yeast, insect cells and lactic acid bacteria whose products are consumed raw to avoid degradation.

Creating 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. Like conventional subunit vaccines, edible vaccines are composed of antigenic proteins and are devoid of pathogenic genes. Thus, they have no way of establishing infection, assuring its safety, especially in immune compromised patients. Edible vaccines activate both mucosal and systemic immunity, as they come in contact with the digestive tract lining. This dual effect would provide first-line defense against pathogens invading through mucosa, like Mycobacterium *tuberculosis* and agents causing diarrhea, pneumonia, STDs, HIV, etc. Scientists place high priority on combating the diarrheal agents.

Norwalk virus, Rotavirus, *Vibrio cholera* and enterotoxigenic *E. coli* (ETEC) .responsible for about three million infant deaths/year, mainly in developing countries.1 Administration of edible vaccines to mothers might be successful in immunizing the *fetus-in-utero* by transplacental transfer of maternal antibodies or the infant through breast milk. Edible vaccines seroconvert even in the presence of maternal antibodies, thus having a potential role in protecting infants against diseases like group-B *Streptococcus*, respiratory syncytial virus (RSV), etc., which are under investigation. Edible vaccines would also be suitable against neglected/rare diseases like dengue, hookworm, rabies, etc. They may be integrated with other vaccine approaches, and multiple antigens may also be delivered. Various foods under study are banana, potato, tomato, lettuce, rice, etc. Edible vaccines are currently being developed for a number of human and animal diseases, including measles, cholera, foot and mouth disease and hepatitis B, C and E.

**Mechanism of Action**

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Edible vaccine mainly stimulates mucosal immunity. This configuration contains both the immune system's innate and adaptive arm (T and B cells). The composition is well structured and these so-called lymphoid mucosal-associated tissues (MALT). SIgA also plays a key role in protecting mucosal surfaces from adhesion for both microbes and toxin activity. The creation of new platforms for the delivery of pathogens or toxin-specific SIgA and systemic IgG is the key to improve vaccine efficacy Microfold (M) cells are one of the major routes of the capture of the antigen at the intestinal level. M cells are a small amount of follicular-associated enterocytes (FAE) which are mainly found in the gastrointestinal tract. These cells capture a wide range of macromolecules from lumens in the small. intestines to antigen submucosal cells (APCs) on Peyer's patches effectively of many APCs, dendritic (DC) cells appear to be the most powerful antigenic cells to trigger an adaptive immune reaction in the priming naive T cells . In an immediate phase, DC is found in a stable state, marked by strong endocytic activity and low capacity for primary naive T cells. DCs, however, mature, increase co-stimulatory molecules and migrate to T-cell areas in lymph nodes under inflammatory situations. There are antigens as well as the release of cytokines to help differentiate the naive antigenspecific T cells into effector cells and migrate to a specific inflammatory site. Intestinal DCs can promote naïve t-cell activation and follicular T-helper differentiation (Tfh) either through direct promotion of Tfh differentiation or through promotion of later transformed T-17 cells into Tfh. Such active B cells leave follicles and move to lymphoid MALT where plasma cells secrete antibodies against immunoglobulin A (IgA) . Those same IgA antibodies are diverted to the lumen in secretions across epithelial cells to interact with antibodies .

**Edible plant vaccines**

Plants started gaining focus as recombinant expression systems in the late 1980's. Plants have a veryimportant advantage over mammalian expression system:they require no external carbon source as they are fueled by photosynthesis. Another major advantage aplant system has on a mammalian system is the absenceof contamination by mammalian pathogens. Theseadvantages specifically make the production of antigens,vaccines, and other eukaryotic proteins in plants more interesting.

**What makes a candidate plant?**

Candidate plants are those plants that are most suitable for edible vaccine production. There are a numberof factors that make a plant a good edible vaccine candidate.

- **Must have long shelf life**:- The plant or the edible part of the plant has to be stored for a long time without degradation. Cereals such as rice, maize, and wheat are great examples of such plants.
- **Must grow quickly**: - Fruits or vegetables that usually are produced on trees are considered bad candidates as they take a long time to grow and mature, whereas plants such as tobacco and tomato have fast growth time. Easy transformation. Plants on which considerable research has been carried out and transformation techniques optimized are very good candidate plants. Plants, unlike other expression systems can be scaled up to need, making it easily available to the masses.

Plants commonly used as candidates Plants with the above-mentioned qualities are generally selected to be edible vaccines. Plants such as tomato, tobacco, rice, and maize are widely used for this purpose. Tobacco was a previously used model plant. It has many advantages such as fast growth, large number of seeds per generation and it is perennial. Tobacco has been used as an edible vaccine candidate extensively. Potatoes are tubers that are widely eaten all around the world and very affordable. A large amount of data on generic manipulation is available, thus making optimized protocols available.

**Tomato**

Tomato is another plant that is widely used and is a popular choice for use as an edible vaccine. It grows relatively quickly and tastes good, thus having a broader range of consumers. The major disadvantage with tomato is that it spoils rapidly after ripening.

**Rice**

Rice is the other plant species used for the development of edible vaccines. Advantages over other plants were commonly used in baby food and high expression of antigen. But it grows slowly and requires glasshouse condition. In 2007, a study conducted in transgenic rice called *Oryzasativa* persuades significant amount of antibodies against E coli. Functional expression of HBs Ag in rice seeds was confirmed in 2008. Vaccines developed from rice plant will have a massive power on the public health where rice is the major source of food.

**Banana**

Banana is the commonly used plant species in the production of edible vaccine. It does not need cooking. Proteins were not destroyed even after cooking. Inexpensive when compared to other plants. Banana plants express HBsAg. The leaf contains antigen. The main disadvantage is it takes 2–3 years to mature and spoils fast after ripening.

**Lettuce**

This plant is an effective model system against enteric diseases in both animals and humans caused by E coli. Glycoprotein E2 expressed lettuce for classical swine fear hog pest virus was developed. This plant is mainly used up in the raw form and it produces beneficial effects against hepatitis B virus. It is the utmost effective plant that can be used as an edible vaccine

**Tobacco**

Tobacco is not an edible plant. It is used as a model for the development of edible vaccines. A vaccine was developed in tobacco for Norwalk virus in 1996 that causes gastroenteritis. Transgenic tobacco expresses VP1 protein against chicken infectious anaemia. Tobacco has the ability to express a polypeptide related to hepatitis B. It is also used to develop vaccine against coccidiosis.

**Alfalfa**

Alfalfa is the plant used to develop edible vaccines mainly for veterinary purposes. Transgenic alfalfa containing hog pest virus glycoprotein E2 was developed in 2005. Alfalfa plants was developed to express Eeg 95-Eg A31 of *Echinococcusganulosus*

**Carrots**

Carrots were not only healthy and delicious but also can be consumed in the form of edible vaccines. Vaccines against HIV, E coli, Helicobacter pylori shows potential effects when it is produced in transgenic carrots. People having weak immune system gets proper benefit by consuming this type of antigen containing carrot edible vaccine

**Challenges**

There are many questions which need to be answered before developing a plant-based vaccine (Table 1). Three successful human clinical trials have shown that adequate doses of antigen can be achieved with plant-based vaccines. To determine the right dosage, one needs to consider the persons weight, age; fruit/plants size, ripeness and protein content. The amount to be eaten is critical, especially in infants, who might spit it, eat a part or eat it all

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and throw it up later. Too low a dose would fail to induce antibodies, and too high a dose would, instead, cause tolerance. Concentrating the vaccine into a teaspoon of baby food may be more practical than administering it in a whole fruit.

**Conclusion**

Edible vaccines are much safer and cheaper alternatives to traditional vaccines. As any edible plant/algae, they can make scaling up so much easier. The problem with edible vaccines is the notion that genetically modified crops are bad, which prevails in many developing nations. With the ever growing and evolving technologies, genetically modified crops are getting safer than ever. There have been reports of laboratory-synthesized meat that can act as replacements for normal meat. In the near future, such meat can also be modified to deliver vaccines of interest upon consumption. With edible vaccines popularized properly and distributed around the world, many diseases can be eradicated and millions of lives can be saved.