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Review Article

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Food Vaccines and their Application in the Treatment of Cancer and COVID-19

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ABSTRACT

Transgenic plants and animals are used to make edible vaccines, which also include immunostimulants. Simply described, edible vaccines are medicines made from plants or animals. Oral vaccinations are more accessible and less expensive in less developed nations. The concept of edible vaccines, in which edible plant parts are used in a vaccine factory, was developed by researchers. Putting desired genes into plants and forcing them to produce the proteins expressed in the genes causes plants to produce edible vaccines. Transgenic plants are the end product of transformation, while plant conversion is the act of transformation. The vaccination that can be eaten fosters mucosal immunity. In the gut, dendritic cells can help native T cells activate and transform into follicular T-helpers (Tfh). A dependable, easily absorbed vaccine will produce exact responses from T and B cells. Many plants are used as substitutes for conventional vaccines, including potatoes, tomatoes, bananas, carrots, tobacco, papaya, algae, and many more. Plant-based vaccinations have been developed for several diseases, including malaria, cholera, hepatitis, rabies, measles, rotavirus, diarrhoea cancer, and covid-19 therapy. Creating and selling edible vaccines takes effort and time. Numerous edible vaccinations for diseases affect animals and people through various stages of clinical testing. In this article, the significance of plant-based immunizations is emphasized.

Keywords: *Food vaccine, Vaccination, Plant-based vaccines, Transgenic plants, Infectious diseases.*

INTRODUCTION

A new era in vaccine administration began in 1998 when researchers supported by the National Institute of Allergy and Infectious Diseases (NIAID) made the first demonstration that an edible vaccine may safely trigger strong immune responses in people. Researchers from Tulane University in New Orleans, the Boyce Thompson Institute for Plant Research in Ithaca, New York, and the University of Maryland in Baltimore collaborated on the study, which was published in the May issue of Nature Medicine.

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"Edible vaccines offer great possibilities for dramatically decreasing the burden of diseases like hepatitis and diarrhoea, particularly in the developing world, where storing and administering vaccinations is often a huge difficulty," said the study (Mor et al., 1999). In 1989, Hiatt and associates suggested creating a plant-based vaccine (Penney et al., 2011). Dr. Arntzen was the pioneer in using transgenic plants to create and deliver monomer vaccines in 1990. The concept of Arntzen showed that an edible vaccine could remove the manufacturing constraints on conventional immunizations. By using tobacco plants (Streptococcus mutants) to express a surface antigen from hepatitis B, they significantly improved the production of edible vaccines (Saxena et al., 2014). Hepatitis B and heat-labile toxin B production in potato and potato plants began concurrently with the production of the edible vaccine in tobacco (Penney et al., 2011).

Concept of Edible / Food Vaccine:

In order to create edible vaccines, desired genes must be inserted into plants, which must then be coerced into producing the proteins expressed in the genes. Transgenic plants are those that have undergone a transformation, and the conversion procedure is referred to as transformation. Like conventional subunit vaccinations, edible vaccines are composed of antigenic proteins and do not contain any harmful genes. As a result, particularly in immunocompromised people, they are unable to initiate infection or guarantee its safety. Conventional subunit vaccines have a poor mucosal response, are expensive and high-tech, and require processing and refrigeration. On the other hand, because they are administered orally, edible immunizations would increase compliance, especially among children, and would lessen the need for skilled medical personnel. Their production process is very effective and adaptable (Webster et al., 2002).

Moms who receive edible vaccines orally may help immunize their unborn children through breast-feeding or transplacental transfer of maternal antibodies. Infants may be protected from illnesses like group B streptococcus, respiratory syncytial virus (RSV), and others thanks to edible immunizations that allow for seroconversion in the presence of maternal antibodies. Edible vaccines are now being produced for a number of human and animal diseases, including cholera, measles, foot-and-mouth disease, and hepatitis B, C, and E. By combining them with other immunization programmes to provide a variety of antigens; they can also be used to prevent uncommon diseases including hookworm, rabies, and dengue fever. For use in ingestible vaccines, tomatoes, rice, banana, lettuce, potato, and a number of other foods are being researched (Giddings et al., 2000).

Eating vaccinations stimulates mucosal and systemic immunity as they meet the digestive tract lining. This dual action would provide first-line defence against pathogens like Mycobacterium tuberculosis and agents that cause pneumonia, STDs, HIV, and other diseases that enter the body through the mucosa. Scientists estimate that three million new-born deaths per year are caused by the diarrheal agents Norwalk virus, vibrio cholerae, rotavirus, and enterotoxigenic E. coli (ETEC), predominantly in developing countries (Landridge et al., 2000).

Mechanism of Edible Vaccine:

The edible vaccination primarily promotes mucosal immunity. This design uses T and B cells to symbolize innate and adaptive immune systems. These MALTs (mucosa-associated lymphoid tissues) are well organized. Additionally, SIgA guards mucosal surfaces from microbial and toxin adherence. The creation of new platforms for the delivery of pathogen- or toxin-specific SIgA and systemic IgG is essential to increasing immunization effectiveness. (Dietrich et al., 2003; & Kunisawa et al., 2012). Microfold (M) cells are one of the most important antigen-capture systems in the gut. They are a particular variety of follicular-associated enterocyte (FAE), which is primarily located in the digestive system. Antigen submucosal cells (APCs) on Peyer's patches to small intestinal canals: These cells can collect various

macromolecules (Mabbott et al., 2013). The most effective cells seem to be dendritic (DC) cells. Antigenic substances stimulate naive T cells to launch an immunological response (Mildner et al., 2014). In the initial phase, DC is observed in a stable form, with High levels of endocytic activity and low levels of primary naive T cell capacity. On the other hand, inflammatory conditions lead to DC development, an increase in co-stimulatory substances, and their movement to T-cell areas in lymph nodes. Antigens and the production of cytokines are employed to help naive antigen-specific T lymphocytes become effector cells and migrate to a specific inflammatory site. (Dalod et al., 2014) Follicular T-helper differentiation (Tfh) and naive T-cell activation can be enhanced by gut DCs, either directly by encouraging Tfh differentiation or indirectly by encouraging Tfh formation in later converted T-17 cells (Shin et al., 2015; & Milpied et al., 2013).

The lymphoid MALT is where active B cells leave the follicle and move, after which plasma cells release antibodies against immunoglobulin A (IgA) (Mishra et al., 2008). To bind with antibodies, the same IgA antibodies are released past epithelial cells and into the lumen (Milpied et al., 2013). DCs can also take up luminous antigens from the epithelial cell layer and then project them into the lumen (Rescigno et al., 2021). A novel method for capturing antigens in the small intestine was the goblet cell, a type of cell involved in the production of mucins (McDole et al., 2012). A reliable, edible vaccine will produce accurate T and B cell responses as well as long-lasting memory cells for future infection outbreaks.

Even though "oral tolerance" refers to the T-cell-mediated paradox of a decrease in specific immune response to previously encountered antigens when administered orally, it was one of the difficulties with oral vaccination administration. (Hernández et al., 2014; & Chan et al., 2015). Because there is little inflammation in the intestinal immune system, antigens are produced there. Juvenile dendritic cells then introduce T cells, leading to the development of resistance. (Lamichhane et al., 2014). In order to alter the tolerogenic process of dendritic cells, regulatory T cells hinder their growth and development. To do this, they produce cytokines like IL-10 and establish close cell-to-cell contact (Richman et al., 1978).

How Food Vaccines are produced:

Proteins and peptides are the two types of antigens that are introduced into the body. Either the entire protein or a peptide portion of the protein serves as the antigen. Utilizing a protein or peptide antigen is a case-specific decision that is influenced by several factors (Hepatitis Foundation, 2022). The two main methods for expressing the immunogenic protein or peptide in the host plant were established using both plant viruses. The first and second are epitope presentation systems and polypeptide expression systems. Epitope presentation methods use "short antigenic peptides fused to the coat protein (CP) that are presented on the surface of formed viral particles. (Pacific Immunology, 2022). Polypeptide expression techniques provide "the complete unfused recombinant protein that accumulates within the plant (Pacific immunology, 2022).

Plant Species Used as Vaccine Mostly:

Banana:

Bananas are the plant species that are most frequently utilized in the production of edible vaccinations. It does not require any preparation. Proteins did not break down even after cooking. It is affordable when compared to other plants. Plants that produce bananas produce HBsAg. The leaf contains antigens. The major disadvantage is that it spoils quickly after reaching maturity, which takes two to three years (Qian et al., 2008).

Rice:

Rice is the second plant species used to make edible vaccines. Being often used in baby food and having a high antigen expression level were advantages over other plants. Nevertheless, it requires the use of a glasshouse and grows slowly. In countries where rice is a major food source, introducing vaccines manufactured from the rice plant will

significantly impact public health (Mason et al., 1996; & Oszvald et al., 2007).

Tomato:

SARS was initially created in tomatoes and is an effective vaccination against acute respiratory illnesses. The Norwalk virus has a stronger antiviral effect (Kumar et al., 2005). Tomatoes were employed to make vaccines for septicemia, pneumonia, and the bubonic plague. It is cultivable in a variety of settings and grows quickly. Vitamin A is abundant in tomatoes and may support your immune system. On the other hand, it spoils rather quickly (Zhang et al., 2006; & Lou et al., 2207)

Potato:

The potato is a useful model for the development of vaccines against the Norwalk virus, diphtheria, tetanus, and hepatitis B. Potato may be used as an oral booster for hepatitis B immunizations in humans (Concha et al., 2017). The ability to easily change and spread potatoes is the main benefit of using them to make edible vaccinations. The main drawback of heat-induced antigen denaturants is that refrigerators are unnecessary for storage (Mason et al., 1996).

Carrot:

In addition to being healthy and delicious, carrots can be used to manufacture edible vaccines. Vaccines against E. coli, Helicobacter pylori, and HIV show potential effects when produced in transgenic carrots. This kind of antigen-containing carrot vaccination is beneficial for people with compromised immune systems (Karasev et al., 2005; Yan-Ju et al., 2010: & Zhang et al., 2010).

Soybean:

The soybean's endoplasmic reticulum (ER) (Glycine max) was used to express the B-subunit of the thermolabile toxin from E. coli bacteria, which produced a total antigen level of up to 2.4 per cent of the total soybean seed protein without any issues after drying for further processing. Additionally, oral administration of this protein to rats causes a rise in systemic IgG and IgA levels. (Takagi et al., 2005; & Saxena et al., 2014).

Algae:

Numerous animal- and human-specific proteins have been produced by the green algae *Chlamydomonas reinhardtii* for medicinal use (Takagi et al., 2005, & Saxena et al., 2014). The entire system can be used as a raw material for the manufacture of edible vaccines because algae grow so quickly. Additionally, algae that are already thriving can be cultivated in bioreactors. *C. reinhardtii* has a single chloroplast, which helps to preserve the appropriate antigens in the algal line. Notably, lyophilization has no effect on the effectiveness of algal vaccines, indicating that the delivery of an edible algae vaccine around the world may be made easier (Concha et al., 2017).

Papaya:

A papaya (Carica papaya) vaccine was developed in 2007 to fight Taenia solium-caused cysticercosis. It was made possible by the production of synthetic peptides in 19 transgenic papaya clones. A 90% immunogenic response was observed in immunized rats during the vaccine trial. The two main carriers of the illness, pigs and humans, may both benefit from these edible immunizations (Sciutto et al., 2002: Sciutto et al., 2011; & Rosales et al., 2019).

Lettuce:

The fact that Lactuca sativa expresses the B-subunit of the thermolabile protein produced by E. coli, which is responsible for both human and animal enteric disease, suggests that this plant may one day serve as an edible vaccine. 2005 saw the expression of glycoprotein E2 from the typical swine fear hog pest virus in lettuce (Spök et al., 2206).

Applications of Food / Edible Vaccines in the Treatment of Several Diseases

Treatment of Covid-19

The broad group of positive-sense implanted RNA viruses known as coronaviruses (COVs) has genomes that range in size from 27 to 32 kb. (Dent et al., 2015). Medicago, a Canadian biopharmaceutical company, was successful in creating viruslike particles (VLPs) of the coronavirus about 20 days after the SARS-CoV-2 genetic sequence. This technology

entails introducing an encoded genetic sequence of COVID-19 spike protein into Agrobacterium, a common soil bacterium that is then consumed by plants, despite employing egg-based vaccine manufacturing techniques (Krenek et al., 2015). A virus-like particle formed of the plant lipid membrane and produced by the arising plant protein increase for COVID-19. Medicago uses a plant called Nicotiana benthamiana, which is in the same family as tobacco plants, to make CoV2 virus VLPs from SARS (Rosales-Mendoza et al., 2020). The recently discovered CoV COVID-19 has not yet been the subject of any approved vaccinations or treatments that have been proven to be successful. As a result of the CoVs infection, which causes a severe respiratory illness with clinical indicators, patients experience acute respiratory symptoms. A CoV vaccine that may be cloned into a transgenic plant like a tomato, cucumber, or lettuce may be made using the Spike (S) protein. After that, the transgenic plants can be consumed as a salad and utilized to immunize people against the recently discovered virus (Kruse et al., 2020).

Anthrax:

The need for a vaccine against Bacillus anthracis has become more pressing, given the likelihood that it could be used as a bioweapon. A protein that is structurally identical to the primary protein present in the existing vaccination might be produced by infusing tobacco leaves with the pag gene (anthrax protection antigen, or PA) using a gene gun. Several billion anthrax antigens could be produced. The edoema and lethal elements that were responsible for the toxic side effects were also absent from this immunization. The same anthrax antigen is now being injected into tomato plants. To create a safer vaccination, scientists are also trying to transform spinach by transfecting it with TMV-expressing PA (Aziz et al., 2002; & Sussman et al., 2003).

Cancer Therapy:

Monoclonal antibodies, which have been proven to be effective cancer therapeutics, are produced effectively by a few plants. For instance, the Monoclonal body (BR-96) is a potent antidote for the chemical doxorubicin, which causes ovarian cancer, breast cancer, lung cancer, and colon tumours in the case of soybeans (Moffat et al., 1995)

Future Prospective of Food / Edible Vaccine:

The idea of a kid receiving a vaccination while eating a tomato (Artnzen et al., 1997) is not outlandish, even though edible immunizations are not currently available thanks to research in disciplines as diverse as agriculture and biotechnology. The idea of transferring an organism's gene into any plant and having that gene produce a new product in any part of the plant, be it the seed, leaf, root, or tuber, is now theoretically possible. Food is becoming recognized as a product with medical benefits in addition to serving as a vital source of sustenance (Kay et al., 1997). A variety of factors influences the future of edible vaccines. Public education about the use and advantages of edible vaccinations is necessary if it is to be widely accepted. The next important criterion to evaluate is the stability of genetically modified plants, and sufficient plant isolation is necessary (Zapanta et al., 2014; & Kim et al., 2016). Future studies and developments on edible vaccines will assess their ability to meet WHO quality standards for purity, potency, efficacy, and safety (Sala et al., 2003). If these immunizations are made available, most diseases might be prevented globally.

CONCLUSION

Vaccines are essential for preventing infections. The creation of an edible vaccine is one of the largest developments in biotechnology. Unlike normal immunizations, edible vaccines can be produced with less expensive tools and machinery. They are less hazardous and do not require sterile storage or injection conditions.

Conventional immunizations are typically administered parenterally, need refrigeration, are prohibitively expensive, and rarely result in mucosal reactions. On the other hand, edible vaccines are less expensive, don't

need to be refrigerated, and promote both systemic and mucosal reactions. A microbiological system is unable to produce complex multimeric proteins, whereas edible vaccines can. In order to produce edible vaccinations, it is vital to carefully monitor the plants that are being grown. Cross-contamination between genetically altered and non-genetically engineered plants is a concern in molecular farming.

Further study and development are required in this area because the benefits of edible vaccinations outweigh the risks, which could usher in a new era of improved control over infectious diseases.

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Competing Interest: **There is no conflict of interest**.

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