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Application of Edible Vaccines

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Abstract. Immunizing humans and animals with edible plants is a developing technique with It appears limitless possibilities. The selected/desired pathogen antigen (HIV, TB, etc.) is injected via the chosen the host plant via the changes procedure as an create a plant that has been altered. Vegetable vaccinations have a lot of potential as a profitable, easy-to-manage, conveniently stored, unlikely or incapable of failure, and sociocultural sustainable option, especially for poor emerging economies. An edible vaccination replaces sore immunization protocols. Compared to conventional vaccines, edible vaccines are less expensive, without needles eliminate the actual need in order to preserve, are safe, might be kept in storage close as an the point of the use, along with provide mucosal layer and whole protection. To enhance human and animal immunity against a variety In viral illnesses, the chosen or preferred antigens The chosen host plant is infected with a variety of viruses, including HIV, TB, etc. There are several different kinds of edible vaccinations under development. to enhance immunity in both people and animals to a variety of infectious illnesses, including hepatitis B, cholera, measles, and FMD. Edible vaccinations can also aid in overcoming autoimmunity illnesses like type 1 diabetes. Edible vaccines have the dual benefit of immunizing generations while also preventing hunger. If the major issues and challenges can be overcome, it will pave the way for more secure and effective immunization

Highlights:

1. Edible vaccines: Cost-effective, needle-free, and easily stored for immunization.
2. Targets diseases: HIV, TB, hepatitis B, cholera, measles, FMD, and more.
3. Potential benefits: Enhances immunity, prevents hunger, and supports global health.

Keywords: Plant-derived vaccines, immunization, future prospective

Introduction

Every year, infectious diseases claim the lives of over a million individuals. Pathogens that infect The mucosal layer of the mammalian host barrier are responsible as well as half among these illnesses (1). Finding novel and distinctive vaccinations that can target diseases and organisms at different stages is the current problem (2). Biological compounds called vaccines increase our immunity. In 1796, Edward Jenner introduced the idea of vaccination for smallpox. The process of vaccination prepares the body to confront and combat novel illnesses. This therapy approach stands in stark

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contrast to the traditional approach, which is typically implemented after a particular ailment has manifested. In addition to protecting us from future infections, vaccines provide long-term immunity to those infections. Up until now, the production process has been the main disadvantage. Since most vaccines are made using industrial methods, they are costly and unavailable in developing nations (2,3). Edible vaccines are therefore thought to be the greatest alternatives to conventional immunizations. Given that edible vaccinations are typically derived from plants that produce antigens, their manufacturing necessitates fundamental. Knowledge of plants and agriculture cultivation (4), furthermore, post-translational alterations that often take place in eukaryotic expression systems may have a positive impact on the immunogenicity of the produced antigen (5,6). These modifications reduce the purifying and downstream processing processes that make conventional vaccines expensive (7). However, post-translational changes do not necessarily increase the vaccine's effectiveness, according to the experiment conducted by Giersing et al. (8). Equal immunogenicity was also demonstrated by protein expression in a prokaryotic system such as E. coli. Even though mammalian systems are costly and extremely challenging to manage, mammalian recombinant expression systems have long been employed to create such proteins (8). They are not a good option for use as a platform for protein expression because of their low expression levels. This is the result of vaccine development. Development of novel, efficient vaccines that protect against a greater range of illnesses

Live-attenuated vaccinations are regarded as the first and original vaccines. Here, a live infectious organism's weakened version serves as a vaccination (9). Inactivated vaccines: are vaccinations that contain the remains of a dead organism. Toxoid vaccines: these use the organism's toxin as a vaccination. Instead of focusing on the virus itself, toxoid vaccinations aim to prevent its negative impacts . The term "biosynthetic vaccines "implies that the vaccinations are produced and closely mimic the pathogenic organism interms of shape along with characteristics. Plasmid DNA with antigen-encoding sequences is used in DNA vaccinations. is used in The DNA vaccinations. After that, Direct access to The muscle or tissue is injected with plasmid DNA (9).

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Action Mechanisms

Action mechanisms of the both immunity and mucosal conformation are primarily stimulated by edible vaccines T and B cells ; the Natural arm In the immune system is adaptable. These so-called lymphoid tissues (MALT) are part of the well-structured composition. SIgA mucosal-associated mucosal is essential for shielding surfaces from microbial and active adherence. The main way to increase vaccine effectiveness is to develop new platforms for delivering toxins to particular SIgA and systemic IgG (10,11). One of the main pathways for the gut level antigen uptake is via microfold (M) cells Among the Follicle-associated enterocytes (FAE), M cells make up a small percentage. Present within the digestive system. The cells effectively collect several different macromolecules from antigen submucosal the patches on Peyer's plate to lumens in the small intestine (12) DC stands for dendritic. Seem to possess the strongest antigenic cells that can prime naive T cells among a variety of APCs in terms of immunological response that is adaptive (13) The DC is observed in a stable condition throughout the initial phase, characterized by limited ability to produce primary naive T cells and high endocytic activity. However, in inflammatory conditions, DCs mature, produce more molecules that act as co-stimulants, and go to the T-cell regions in nodules of lymph. To enable naive T lymphocytes that are specific to antigens to develop into cells that serve as effectors and proceed. up to a certain provocative The place , there are antigens as well as cytokine publication (14). Through direct or indirect promotion of Tth differentiation, , intestinal DCs can stimulate naivete - Cell activation and the development of follicular T-helpers (Tfh) by encouraging T-17 cells that have subsequently changed into Tfh (15,16) After leaving follicles, these active B cells travel to MALT in lymphoid cells, where plasma release antibodies called Immunoglobulin A (IgA) (16). To interact with antibodies, those that are against the same Transport of IgA antibodies by secretions from the lumen's epithelial cells (17). Additionally, DCs can be selectively acquire luminous antigens via the layer of epithelial cells, followed by project entering the lumen via dendrites (18). A more modern method of absorbing athe small intestine's antigen intestine was the goblet cell, a kind of cell that performs mucin production. Goblet cells have the ability to guide absorb along with deliver digestive antigens , as demonstrated by intravitreal microscopy (19). A dependable, consumable vaccination will cause certain reactions in B and T cells, which will furthermore help

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create cells of memory that last for later meetings during the actual infection. Among the arguments surrounding oral vaccination management was the development regarding "oral tolerance," which refers to the contradiction caused via T cells that involve a reduction within the particular immunological reaction to earlier experienced antigen via the oral pathway (20,21). Because there is less inflammation, the intestinal immune system releases antigens, and developing dendritic cells bring in T cells, which create tolerance because there is less inflammation, the intestinal immune system releases antigens, T lymphocytes are introduced by immature dendritic cells, resulting in tolerance. create tolerance (21). Cell-to-cell close contact and secreted cytokines like IL-10 happen when regulatory T cells stop dendritic cells from growing and developing to change their tolerogenic mechanism (22). The immune response in humor may also be suppressed by repeated injections of mucous antigens, and it is challenging to create vaccinations with consistent amounts (23)(figure.1)

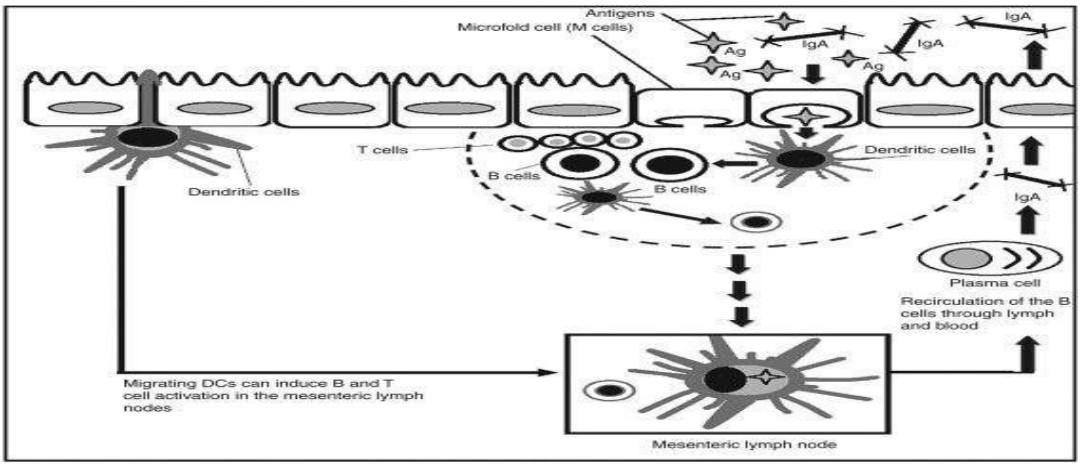

Figure.1: Edible vaccines' mode of action (24)

Production of edible vaccines

Manufacturing of Vaccines That Are Edible Transgenes can be incorporated into certain plant cells to create edible vaccinations. Either the direct delivery of genes approach or the method of indirect gene delivery can be used to integrate the transgene without mixing it with the vector depending on the antigen's location the transgene can be used with the cells to express in plants that use either of two change systems (stable transformation or transient system of transformation (25-26)

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Direct Method of Gene Delivery

Method of Gene Delivery Directly The straightforward approach is direct gene delivery. This involves directly introducing the selected DNA or RNA into the plant cell. The biological approach, usually the gene gun, also referred to as the bombardment with microprojectiles technique, is the most widely utilized direct gene delivery technique. This approach is independent of vectors. Method of direct gene delivery. Feasible, this is carried out (27–28). In this type of transformation, tungsten is applied to the DNA or RNA to serve as A micro-carrier. After that, The genetic material that has been coated is put inside the gene gun and exposed to high levels of pressure of helium gas. Due to the strong pressure, the DNA coating will move and enter the plant cell that is being targeted. This technique can damage the plant and is quite expensive. (29–30) the application of the biolistic approach can transform the nuclear and chloroplasts. The two categories of Various antigen expression techniques were as follows (31). the process of nuclear transformation is introducing a desired gene into the plant cell's Chloroplast transformation is the process of introducing the gene into the chloroplast to increase the protein production, whereas nucleus through non-homologous recombination Transformation of chloroplasts is the most extensive used technique for creating edible vaccines. (32–33) The rotavirus, canine parvovirus, cholera, Lyme disease, anthrax, tetanus, and plague. are a few examples of vaccines made using biolistic techniques. (34).

Indirect Gene Delivery

Gene Delivery Through Indirect Means This gene delivery method is vector-mediated. Using this technique, the target A plant virus-infected plant cells. Virus or bacteria to generate the desired protein (35) (figure.2).

Figure 2. Diagram illustrating different processes for producing edible vaccines derived from plants (36).

Applications of Edible Vaccines

The cancer treatment: Numerous plants have been effectively altered in order to generate monoclonal antibodies that are efficient agents for cancer treatment. In the

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instance of soybeans, as well as instance, The monoclonal body BR-96 works well. Agent that aims to the drug Doxorubicin, which is causes tumors of the lung, colon, ovarian, and breast cancer (37).

Birth control: TMV administration results in the production of ZB3 protein, a protein present in Mousezonapellucida that can stop mice's eggs from fertilizing because of the antibodies it creates (37).

Chloroplast transformation:

Because of the nature of maternal inheritance Chloroplast genomes are not able to be passed on to plants through normal pollination across borders. However, it may help spread and accumulate in large amounts as transgenic protein (38).

Function in autoimmune disorders:

The synthesis of self-antigens in plants is being scaled up in response to autoimmune illnesses in their developmental stages. Among the conditions being researched include lupus, rheumatoid arthritis, multiple sclerosis, and study transplant rejection. A clinical strain of mice that were fed potatoes as an those with diabetes. Potatoes that expressed both a protein and insulin known as GAD, or the decarboxylase of glutamic acid , which is connected The component of CT-B. The protein is efficient in preventing assaults by the immune system and postponing the development of elevated levels of blood sugar (39).

Recombinant Proteins and Medications:

In addition to being significant producers of vaccines and antibodies, engineered viral inoculations change the composition of plants to create medications (albumin, serum protease, and interferon), enzymes, such as glucocerebrosidase (hGC) interleukin-10 to treat Crohn's illness and in tobacco plants to treat Gaucher's disease. This production approach lowers the price by a factor of ten thousand (40). Commercial products of the process of producing recombinant therapeutic proteins from plants include trichosanthin (a ribosome activator), Angiotensin-I antihypertensive medication, and hirudin, an antithrombin-antiviral protein that suppresses HIV in vitro (40).

Principal plant species that serve as models for vaccines

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Tobacco: It is not possible to eat tobacco. It functions as a prototype for the advancement of of an edible vaccination. A vaccination was created in 1996. The virus known as Norwalk, which results in gastrointestinal illness, was produced using tobacco. Transgenic tobacco expresses the VP1 protein to prevent hens with contagious anemia. A polypeptide linked to the hepatitis B virus can be produced through tobacco. In addition, it is used in the development of a vaccination against coccidiosis (41-42).

The potato: The potato is a suitable model for creating vaccines against the Norwalk virus, hepatitis B, diphtheria, and tetanus. The initial effort to create a potato-based edible vaccine targets E. coli-induced gastroenteritis. Additionally, potatoes may be a substance that strengthens the teeth for human vaccinations against hepatitis B (43).

Rice: The other plant species used to create edible vaccinations is rice. Advantages over other plants featured widespread use and elevated antigen expression in baby feeding. But it needs the glasshouse conditions along with development gradually. Research from a 2007 study found that Oryza sativa, a transgenic rice, produces a sizable amount of anti-E. Coli antibodies. It was discovered in 2008 that rice seeds exhibited functional expression of HBsAg. In areas where rice is a major food source, vaccines from the rice plant will significantly affect the general public's health (44–45

Banana: The banana is a plant species that is frequently used to make edible vaccines. It doesn't require cooking. Despite being cooked, proteins remained intact. Cheap with other plants. In banana plants, HBsAg is expressed. This leaf has antigen Its primary drawbacks are that it takes two to three years to mature and that it degrades quickly after ripening (46).

Tomato: It was the first plant to produce an effective vaccination against coronavirus-induced acute respiratory syndrome, or SARS. Compared to vaccinations made from, it has a stronger influence on the Norwalk virus. The stem leaves, fruits as well as additional tissues possess the capacity to produce CT-B proteins derived from toxins from Vibrio cholera B (47).

The lettuce: This plant works well as a model system to prevent E. coli-induced intestinal illnesses in both people and animals. For the classical E2-expressed lettuce glycoprotein, The virus that causes swine fear hogs was created. This plant has positive

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benefits against the virus that causes hepatitis B and is mostly consumed uncooked. It is the best plant for use as an edible vaccination (48–49) (figure.1 & figure .2).

Fruit/ Plant	Main Features	Advantage	A disadvantage
Potato	It has been utilized to deliver diabetes-related proteins, cholera vaccines, Norwalk virus vaccines, and vaccines against a type of E. Coli.	- Controlled clinical studies - Easily altered or changed - Easily spread from its "eyes" - Long-term storage without refrigeration Cooking potatoes does not always eliminate an antigen's complete complement	Cooking is necessary because it can denature the antigen and reduce its immunogenicity.
Banana	The primary factor making bananas an excellent option for an edible vaccination is their sterility, which prevents genes from spreading from one banana to another	- They don't require cooking -Cooking doesn't degrade the protein · -They are inexpensive ·-They are grown extensively in underdeveloped nations They develop swiftly - - They contain a lot of vitamin A, which could make the immune system stronger	It takes two to three years for trees to mature; transformed trees take around a year to yield fruit; they spoil quickly following ripening; and they have minimal amount of protein, making them unlikely to create a lot of recombinant proteins

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Tomato	a potential edible vaccine to prevent respiratory syncytial virus SARS, anthrax, rabies, norovirus, Alzheimer's, hepatitis B, and HIV/AIDS. the initial instance, a foreign gene was inserted Enter the chloroplasts or plastids	- Rapid growth - widespread cultivation - high vitamin A content that may strengthen the immune system - Take advantage of freeze-drying technologies to solve the spoiling issue. - Powders that contain antigens and are heat stable that are formed into capsules - Blended from several batches to provide consistent antigen dosages -Reduces the risk of infection transmission - Does not require special storage or shipping facilities - They have a nice flavor	Easily spoils

Alfalfa: The vegetation utilized to make vaccinations that are edible, primarily for veterinary use, the alfalfa. In 2005, alfalfa transgenic with Glycoprotein E2 of the hog pest virus was created. Alfalfa plants were created to express Echinococcus ganulosus's Eeg95-EgA31 (42).

Carrots: in addition to being tasty and nutritious, carrots can be utilized in the production of edible vaccines. Transgenic carrots have the potential to create vaccines against Helicobacter pylori, E. coli, and HIV. This kind of antigen-containing carrot consumable vaccination is beneficial for people with weakened immune systems (50–51).

Table 1: Some important Plants that are used as Edible vaccines (59).

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Table 2: Some of the main vaccines and their vehicles, for humans and animals, explored to date (60).

vaccination against	Vehicle
Human hepatitis B	Lettuce, tobacco, maize, bananas, and tomatoes
Human Rabies Virus	Tomato and Tobacco
Human enterotoxigenic E. coli	Maize, Potato, and Tobacco
Cholera, or Vibrio cholerae, in humans)	Potato
Human Norwalk Virus	Tumor, Potato, and Tobacco
Human stomach virus	Potato
HIV in humans	Spinach, Arabidopsis, and tomato
Human cervical cancer	Tobacco
Human Crohn's disease	Tobacco
Human Alzheimer's disease	Tomato
Insulin	Potato and Arabidopsis
Human SAARS	Tomato and Milk
Human measles	Tobacco
The human cytomegalovirus	Tobacco
A virus that causes hemorrhage in rabbits	Potato
Foot-Mouth disease in domestic agriculture animals	The Arabidopsis and Alfalfa
Coronavirus-transmittable gastroenteritis in pigs	Maize, tobacco, and Arabidopsis

Advantages of Edible Vaccines

1- Since edible vaccines don't need to be kept in a cold chain like conventional vaccinations do, they are relatively inexpensive (52).
2- Because transgenic plant seeds have a lower moisture content and are easier to dry, edible vaccines provide more storage options. Furthermore, plants that produce oil or their aqueous extracts have greater storage potential (53).
3- Unlike conventional injectable vaccines, edible vaccines are commonly accepted because they are taken orally. Because They don't require the buildings and production space to be sanitized, they do away with the necessity for qualified medical professionals and lower the danger of contamination (54).

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Disadvantages of Edible Vaccines

1- Certain foods must be cooked before consumption, which may denature the vaccination protein and lessen or even eliminate its immune-stimulating properties (55).
2- Up until now, scientists have struggled to get high expression levels of the chloroplast gene found in the plant's edible sections (56)
3- Infants find it inconvenient (57).
4- Because vegetables like tomatoes and bananas don't come in normal amounts, people might eat too much vaccination, which could be harmful, or too little, which could cause a disease epidemic among the population that is thought to be immune (58).

References

[1] I. Espinosa, J. J. Rosero, J. L. Gonzalez, J. C. Urresty, and J. Riba, "Wavelet denoising for impedance-based fault location in underground distribution networks," IEEE Transactions on Power Delivery, vol. 37, no. 4, pp. 3144-3153, Aug. 2022, doi: 10.1109/TPWRD.2022.3155226.

[2] R. A. Jabr, "Optimization of AC-DC hybrid distribution networks: A review," IEEE Transactions on Smart Grid, vol. 10, no. 1, pp. 173-183, Jan. 2019, doi: 10.1109/TSG.2017.2752227.

[3] B. Parkhideh and S. Bhattacharya, "A novel approach to interconnecting single-phase sources with three-phase utility systems," IEEE Transactions on Industrial Electronics, vol. 60, no. 3, pp. 1244-1255, Mar. 2013, doi: 10.1109/TIE.2012.2188253.

[4] L. K. Gan, N. Liu, and Y. Tang, "Reliability evaluation of power distribution networks considering protection failures," IEEE Transactions on Power Systems, vol. 33, no. 3, pp. 2635-2646, May 2018, doi: 10.1109/TPWRS.2017.2734180.

[5] A. M. Leite da Silva, L. A. da Fonseca Manso, R. Billinton, and M. J. V. Todorovic, "Comparison of time sequential and state enumeration simulation for reliability

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.104

evaluation of composite generation and transmission systems," IEEE Transactions on Power Systems, vol. 15, no. 1, pp. 73-80, Feb. 2000, doi: 10.1109/59.852118.

[6] Y. Zhang, H. Wen, J. J. Gu, and D. H. Xu, "A novel hierarchical protection scheme for DC microgrids," IEEE Transactions on Smart Grid, vol. 9, no. 5, pp. 5058-5068, Sep. 2018, doi: 10.1109/TSG.2017.2668560.

[7] S. S. Koury and M. K. Khalil, "Intelligent fault diagnosis system for power distribution networks," IEEE Transactions on Power Systems, vol. 22, no. 3, pp. 1145-1155, Aug. 2007, doi: 10.1109/TPWRS.2007.901660.

[8] J. Z. Wang, X. Y. Zhang, and Y. H. Song, "Advanced fault diagnosis techniques for modern power systems," IEEE Transactions on Smart Grid, vol. 10, no. 4, pp. 4562-4574, Jul. 2019, doi: 10.1109/TSG.2018.2880716.

[9] M. Fotuhi-Firuzabad and R. Billinton, "Reliability evaluation of electric power systems using Monte Carlo methods," IEEE Transactions on Power Systems, vol. 14, no. 4, pp. 1266-1272, Nov. 1999, doi: 10.1109/59.801883.

[10] C. L. Su and Y. L. Kuo, "Application of artificial intelligence in distribution system reliability assessment," IEEE Transactions on Power Systems, vol. 22, no. 4, pp. 1897-1905, Nov. 2007, doi: 10.1109/TPWRS.2007.907444.

[11] J. Kunisawa et al., "GU associated lymphoid tissues for the development of oral vaccines," Adv. Drug Deliv. Rev., vol. 64, no. 6, pp. 523–530, 2012.

[12] N. A. Mabbott et al., "Microfold (M) cells: Important immunosurveillance posts in the intestinal epithelium," Mucosa Immunol., vol. 6, pp. 666–667, 2013.

[13] A. Mildner and S. Jung, "Development and function of dendritic cell subsets," Immunity, vol. 40, pp. 642–646, 2014.

[14] M. Dalod et al., "Dendritic cell maturation: Functional specialization through signaling specificity and transcriptional programming," EMBO J., vol. 33, pp. 1104–1116, 2014.

[15] C. Shin et al., "CD8α—Dendritic cells induce antigen-specific T follicular helper cells generating efficient humoral immune responses," Cell Rep., vol. 11, pp. 1929–1940, 2015.

[16] P. J. Milpied and M. G. McHeyzer-Williams, "High-affinity IgA needs TH17 cell function plasticity," Nat. Immunol., vol. 14, pp. 315–313, 2013.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.104

[17] M. Rescigno et al., "Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria," Nat. Immunol., vol. 2, pp. 361–366, 2001.

[18] J. R. McDole et al., "Goblet cells deliver luminal antigen to CD103+ DCs in the small intestine," Nature, vol. 483, pp. 345–349, 2012.

[19] M. Hernandez et al., "Transgenic plants: A 5-year update on oral antipathogen vaccine development," Expert Rev. Vaccines, vol. 13, pp. 1523–1536, 2014.

[20] H. T. Chan and H. Daniell, "Plant-made oral vaccines against human infectious diseases—Are we there yet?" Plant Biotechnol. J., vol. 13, pp. 1056–1070, 2015.

[21] A. Lamichhane, T. Azegami, and H. Kiyono, "The mucosal immune system for vaccine development," Vaccine, vol. 32, pp. 6723–6711, 2014.

[22] L. K. Richman et al., "Enterically induced immunologic tolerance. I. Induction of suppressor T lymphocytes by intragastric administration of soluble proteins," J. Immunol., vol. 121, pp. 2429–2434, 1978.

[23] M. Lesik-Brodacka et al., "The immune response of rats vaccinated orally with various plant-expressed recombinant cysteine proteinase constructs when challenged with Fasciola hepatica metacercariae," PLoS Negl. Trop. Dis., vol. 11, 2017.

[24] S. Bhatia and R. Dahiya, "Modern applications of plant biotechnology in pharmaceutical sciences," 2015.

[25] J. L. Clarke et al., "Lettuce-produced hepatitis C virus E1E2 heterodimer triggers immune responses in mice and antibody production after oral vaccination," Plant Biotechnol. J., vol. 15, no. 12, pp. 1611–1621, 2017.

[26] M. N. Madhumita et al., "Edible vaccines—A review," Int. J. Pharmacother., vol. 4, pp. 58, 2014.

[27] C. Fauquet et al., "Particle bombardment and the genetic enhancement of crops: Myths and realities," Mol. Breed., vol. 15, no. 3, pp. 305–327, 2005.

[28] Q. Chen and H. Lai, "Gene delivery into plant cells for recombinant protein production," BioMed Res. Int., 2015. DOI: 10.1155/2015/932161.

[29] H. S. Mason et al., "Expression of hepatitis B surface antigen in transgenic plants," Proc. Natl. Acad. Sci. USA, vol. 89, pp. 11745–11749, 1992.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.104

[30] E. Gomez, "Developments in plant-based vaccines against diseases of concern in developing countries," Open Infect. Dis. J., vol. 4, no. 2, pp. 55–62, 2010.

[31] T. Kim and M. Yang, "Current trends in edible vaccine development using transgenic plants," Biotechnol. Bioprocess Eng., vol. 15, no. 1, pp. 61–65, 2010.

[32] C. P. Shah et al., "Edible vaccine: A better way for immunization," Int. J. Curr. Pharm. Res., vol. 3, no. 1, pp. 1–4, 2011.

[33] T. Arakawa et al., "Expression of cholera toxin B subunit oligomers in transgenic potato plants," Transgenic Res., vol. 6, no. 6, pp. 403–413, 1997.

[34] L. Wu et al., "Expression of foot-and-mouth disease virus epitopes in tobacco by a tobacco mosaic virus-based vector," Vaccine, vol. 21, no. 27–30, pp. 4390–4398, 2003.

[35] H. Esmael and E. Hirpa, "Review on the edible vaccine," Acad. J. Nutr., vol. 4, no. 1, pp. 40–49, 2015.

[36] W. H. R. Langridge, "Edible vaccines," Sci. Am., vol. 283, no. 3, pp. 66–71, 2000. DOI: 10.1038/scientificamerican0900-66.

[37] A. S. Moffat, "Exploring transgenic plants as a new vaccine source," Science, vol. 268, pp. 660, 1995.

[38] H. Daniell, M. S. Khan, and L. Allison, "Milestones in chloroplast genetic engineering an environmentally friendly era in biotechnology," Trends Plant Sci., vol. 7, no. 9, pp. 191, 2002.

[39] T. Arakawa et al., "A plant-based cholera toxin B subunit-insulin fusion protein protects against the development of autoimmune diabetes," Nat. Biotechnol., vol. 16, pp. 934–938, 1998.

[40] C. S. Prakash, "Edible vaccines and antibody-producing plants," Biotechnol. Develop. Mon., vol. 27, pp. 10–13, 1996.

[41] J. S. Yang et al., "Expression of hemagglutinin-neuraminidase protein of Newcastle disease virus in transgenic tobacco," Plant Biotechnol. Rep., vol. 1, pp. 85–92, 2007.

[42] D. M. Pérez Filgueira et al., "Protection of mice against challenge with foot and mouth disease virus (FMDV) by immunization with foliar extracts from plants infected with recombinant tobacco mosaic virus expressing the FMDV structural protein VP1," Virology, vol. 264, no. 1, pp. 85–91, 2002.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.104

[43] C. Concha et al., "Disease prevention: An opportunity to expand edible plant-based vaccines," Vaccine, vol. 5, no. 2, pp. 14–23, 2017.

[44] H. S. Mason, "Expression of Norwalk Virus Capsid Protein in Transgenic Tobacco and Potato and Its Oral Immunogenicity in Mice," Proc. Natl. Acad. Sci. USA, vol. 93, pp. 5335–5340, 1996.

[45] M. Oszvald, et al., "Expression of a Synthetic Neutralizing Epitope of Porcine Epidemic Diarrhea Virus Fused with Synthetic B Subunit of Escherichia coli Heat-Labile Enterotoxin in Rice Endosperm," Mol. Biotechnol., vol. 35, p. 215, 2007.

[46] B. Qian, et al., "Immunogenicity of Recombinant Hepatitis B Virus Surface Antigen Fused with PreS1 Epitope Expressed in Rice Seeds," Transgenic Res., vol. 17, pp. 621–631, 2008.

[47] G. B. S. Kumar, et al., "Expression of Hepatitis B Surface Antigen in Transgenic Banana Plants," Planta, vol. 222, no. 3, pp. 484–493, 2005.

[48] L. Srinivas, et al., "Transient and Stable Expression of Hepatitis B Surface Antigen in Tomato (Lycopersicon esculentum L.)," Plant Biotechnol. Rep., vol. 2, pp. 1–6, 2008.

[49] T. G. Kim, et al., "Synthesis and Assembly of Escherichia coli Heat-Labile Enterotoxin B Subunit in Transgenic Lettuce (Lactuca sativa)," Protein Expr. Purif., vol. 51, no. 1, pp. 22–27, 2007.

[50] Y.-J. Ye and W.-G. Li, "Immunoprotection of Transgenic Alfalfa (Medicago sativa) Containing Eg95-EgA31 Fusion Gene of Echinococcus granulosus Against Eg Protoscoleces," J. Trop. Med., vol. 3, pp. 10–13, 2010.

[51] H. Zhang, et al., "Oral Immunogenicity and Protective Efficacy in Mice of a Carrot-Derived Vaccine Candidate Expressing UreB Subunit Against Helicobacter pylori," Protein Expr. Purif., vol. 69, pp. 127–131, 2010.

[52] T. Nochi, H. Takagi, Y. Yuki, L. Yang, T. Masumura, M. Mejima, et al., "Rice-Based Mucosal Vaccine as a Global Strategy for Cold-Chain- and Needle-Free Vaccination," Proc. Natl. Acad. Sci. USA, vol. 104, pp. 10986–10991, 2007.

[53] D. W. Pascual, "Vaccines Are for Dinner," Proc. Natl. Acad. Sci. USA, vol. 104, pp. 10757–10758, 2007.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.104

[54] S. J. Streatfield, J. M. Jilka, E. E. Hood, D. D. Turner, M. R. Bailey, J. M. Mayor, et al., "Plant-Based Vaccines: Unique Advantages," Vaccine, vol. 19, pp. 2742–2748, 2001.

[55] E. Ferrante, D. Simpson, and T. Scott, "A Review of the Progression of Transgenic Plants Used to Produce Plantibodies for Human Usage," J. Young Investigators, vol. 4, no. 1, Jun. 2001.

[56] D. Kingsley, "Eat Your Reds," ABC Science Online [Internet], Sep. 7, 2001. Available: http://www.abc.net.au/science/articles/2001/09/07358312.htm

[57] "A Review of the Progression of Transgenic Plants Used to Produce Plantibodies for Human Usage," J. Young Investigators, vol. 4, 2001.

[58] M. Pawar, K. Nikam, and R. Arutkar, "Edible Vaccine - A Great Boon in Medicinal Science," PharmaTutor [Internet]. Available: http://www.pharmatutor.org/articles/edible-vaccine-a-great-boon-in-medicinal-science

[59] "A Review of the Progression of Transgenic Plants Used to Produce Plantibodies for Human Usage," J. Young Investigators, vol. 4, 2001.

[60] "Molecular Farming of Edible Vaccines" [Internet], 1998–2001. Available: http://molecularfarming.com/ediblevaccine.html