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A Review on Edible Vaccines: A Novel Approach to Oral Immunization

Dhiraj Pawar, Rushikesh Kadam, Tushar Gaikwad
Appasaheb Birnale college of pharmacy, Sangli, Maharashtra
Late. N.B. Chabada college of pharmacy, Satara, Maharashtra
Assistant professor at, Late. N.B. Chabada college of pharmacy, Satara, Maharashtra

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ABSTRACT: Plant-based Edible Vaccines are a low-cost, easy-to-use, storable, and commonly accepted vaccine delivery strategy, particularly in underdeveloped nations. Human trials undertaken by the US Department of Health and Human Services' National Institute of Allergy and Infectious Diseases (NIAID) suggest that edible vaccinations are possible. A vaccine against viral diseases of hepatitis and transmissible gastroenteritis virus has been patented by Prodi Gene, a biotech business. Plant-based Edible Vaccines are subunit vaccines that insert certain genes into plants to help them produce encoded protein. Edible vaccines based on plants are now being developed for a variety of human and animal ailments. Transgenic crops are in higher demand in both developed and poor countries. The focus of this review is on conception. The focus of this review is on the conceptualization of plant-based consumable vaccines, as well as their mechanism and manufacture.

KEYWORDS: Plant-based Edible vaccine, transgenic crops, mucosal targeted vaccines, plant expression host.

I. INTRODUCTION

In 1990, Charles Arnzen, Hugh Mason, and colleagues initially used the phrase “edible vaccines." They are mucosal targeted vaccines that stimulate both systemic and mucosal immune responses, making them one of the safest and most successful ways to manage infectious diseases such as cholera, easels and hepatitis B and among others. These vaccines are also used to suppress disorders such as diarrhoea, Type 1 diabetes, rheumatoid arthritis, etc. [1]

The concept of plant molecular farming was quickly developed after the proof of concept for recombinant plant-derived pharmaceutical proteins was reported and published, the idea of plant molecular farming grew swiftly, and it has now spread to the synthesis of several industrial and agricultural recombinant enzymes. [2] The main goal of this technology is to create an edible vaccine that protects against a variety of diseases by eliciting a specific immune response after oral administration and uptake of a plant-based edible vaccine.[3]

The first transgenic tobacco to express human growth hormone was synthesized in 1986. Another research group later developed transgenic tobacco in 1989 that expressed an antibody with the correct assembly of functional complex glycoproteins. [4] Mason et al. demonstrated the structural validation of recombinant protein in 1992 by generating the hepatitis B virus (HBV) surface antigen (HBsAg) in tobacco plants. [5]

Plant-based edible vaccines are made by introducing desired genes into plants and then forcing the transformed plants to produce the encoded proteins. Transgenic plants are the result of this process, which is known as transformation. As they come into contact with the digestive tract lining, plant-based edible vaccines activate both mucosal and systemic immunity. This dual-action would serve as a first-line defence against pathogens that assault the mucosa, such as Mycobacterium tuberculosis and agents that cause diarrhoea, pneumonia, STDs, HIV, and other diseases. Scientists are focusing their efforts on the diarrheal agents Norwalk virus, Rotavirus, Vibrio cholera, and enterotoxigenic E. coli (ETEC), which cause over 3 million baby deaths each year, mostly in developing nations.[6]

Plant-based vaccines given to pregnant women may be effective in immunising the foetus in the uterus through transplacental transfer of maternal antibodies or the baby through breast milk. Edible vaccines induce seroconversion in the presence of maternal antibodies, potentially protecting children against diseases such as group-B Streptococcus, respiratory syncytial virus, and other diseases now under investigation. Plant-based edible vaccines could also be used to prevent diseases

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including dengue fever, hookworm, and rabies. They can be combined with other vaccine techniques, and they can deliver several antigens. Banana, potato, tomato, lettuce, rice, and other foods are among those being investigated. Measles, cholera, hepatitis B, C, and We are among the illnesses for which edible vaccines are now being produced.[7]

Advantages- [8]

1. Easy to administer.
2. Medical personnel are not required.
3. There is no longer a need for sterile injection circumstances.
4. cost-effective in mass production.
5. Administration and transportation are simple.
6. Effective vaccine activity maintenance through plant temperature control cultivation.
7. Pathogens and poisons are not present in therapeutic proteins.
8. Storage near the place of usage
9. Heat resistant, obviating the necessity for refrigeration.
10. Bioencapsulation provides antigen protection.
11. Improved safety due to subunit vaccination (not attenuated vaccine).
12. No major adverse effects have been reported as of yet.
13. Better compliance (especially in children).
14. Multiple antigen delivery
15. Combination with other vaccine strategies.

Disadvantages-[8]

1. Dosage consistency varies significantly from fruit to fruit, plant to plant, lot to lot, and generation to generation.
2. The vaccine's stability in fruit is unknown.
3. Dosage requirement evaluation is time-consuming.
4. It is difficult to choose the best plant.
5. Certain foods, such as potatoes, should not be consumed uncooked since heating them weakens the medicine they contain.
6. Inconvenient for infants since they may spit it out, consume a portion or all of it, and then puke it up later. It may be more practical to concentrate the vaccination into a teaspoon of baby food rather than giving it as a whole fruit.
7. Because the vaccination and the vehicle interact, there is always the chance of side effects.

Limitations-[9,10,11]

1. Because edible vaccines are still in their early stages, there are many unknowns to be discovered.
2. The appropriate dosage amount and duration are still unknown. Many factors influence the dosage, including plant generation, individual plant, protein content, ripeness of the fruit, and how much is consumed.
3. The dosage fluctuates due to the difficulties of standardising the antigen concentration in plant tissue; it might be time-consuming to manufacture consistently and in large quantities.
Individual fruits on a plant, individual plants, and plant generations can all have large differences in antigen concentration.
4. Low doses result in less antibody consumption, whilst large doses result in antibody establishment.

Table no. 1: Traditional Vaccines Vs Edible vaccines. [12,13]

Traditional vaccines	Edible vaccines
Too expensive	Comparatively Less expensive.
This vaccine cannot be distributed due to a lack of physical infrastructure.	May be easily available.
Required skilled persons to administer vaccines	Do Not required skilled persons to administer vaccines.
Refrigeration is required.	Refrigeration is not required.
Needles and syringes are required.	Needles and syringes are not required.
The immune system cannot be stimulated directly.	The immune system stimulates directly.

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II. PRODUCTION OF PLANT-BASED EDIBLE VACCINES

1. Direct gene delivery method:

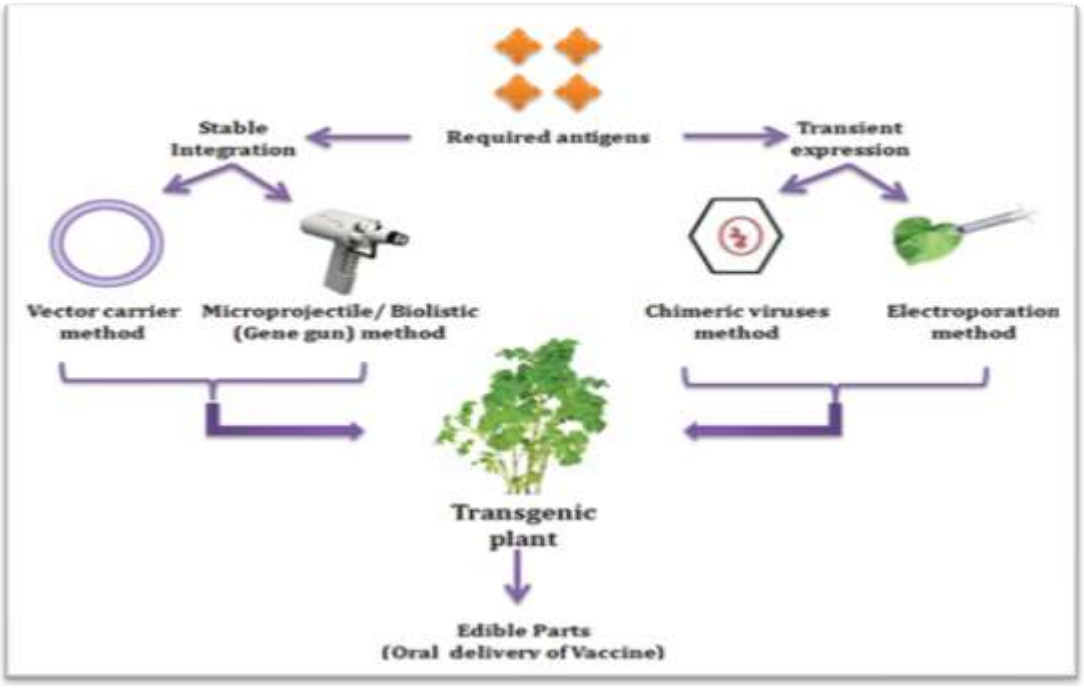
This is the most straightforward method. The chosen DNA or RNA is directly delivered into the plant cell in this method. The most often used. The biolistic approach, also known as a gene gun, is a commonly used direct gene delivery method. Or the method of micro-projectile bombardment. This approach is vector-independent. This is used When gene transfer by agrobacterium species-mediated transformation fails. Examples of vaccines produced by biolistic methods are cholera, Lyme disease, anthrax, tetanus, plague, Rotavirus and canine parvovirus. [14,15,16]

2. Indirect delivery method:

The vector-mediated gene delivery approach is an indirect delivery method. To create the protein of interest, the desired plant cells were infected with plant bacterium or plant virus.[17]

Agrobacterium-mediated Gene transfer-

Agrobacterium is a gram-negative bacterium that attacks plants and transfers its genes to the nucleus of the plant. The two most usually employed species are Agrobacterium tumefaciens and Agrobacterium rhizogenes. The tumour-inducing Ti plasmid is carried by Agrobacterium tumefaciens, while the root-inducing Ri plasmid is carried by Agrobacterium rhizogenes.[18]



Schematic diagram showing various methods of production of plant-based edible vaccines

III. MAJOR PLANT SPECIES USED AS VACCINE MODELS

Tobacco-

Tobacco is not a plant that can be eaten. It's being used to develop edible vaccines as a model. In 1996, a vaccine for the Norwalk virus, which causes gastroenteritis. VP1 protein is expressed in transgenic tobacco to protect chickens from infectious anaemia. Tobacco can produce a hepatitis B-related polypeptide. It's also utilised to create a coccidiosis vaccine. [20,21,22}

Potato-

Potato is a good model for developing vaccines for tetanus, diphtheria, hepatitis B, and the Norwalk virus. The first attempt to make an edible vaccination in potatoes was for E. coli enteritis. In humans, potatoes may serve as an oral strengthening agent for hepatitis B vaccinations.[23]

Rice-

Rice is another plant species that has been utilized to make edible vaccinations. Advantages over other plants were widespread use in baby food and strong antigen expression. However, it grows

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slowly and requires a glasshouse. In 2007, research on Oryza sativa, transgenic rice, persuaded a substantial number of antibodies against E Coli. In 2008, the functional expression of HBsAg was confirmed in rice seeds. Vaccines made from rice plants will have a huge impact on public health in areas where rice is a key food source. [24,25]

Banana-

The banana is the most common plant species utilized to make edible vaccines. There is no need to cook it. Even after cooking, proteins were not damaged. When compared to other plants, it is inexpensive. HBsAg is produced by banana plants. An antigen is present in the leaf. The biggest drawback is that it takes 2–3 years to mature and destroys quickly once ripe.[26]

Tomato-

SARS, a coronavirus-causes acute respiratory infection, was first discovered in tomatoes and developed into a vaccine. It is more effective against the Norwalk virus than vaccines made from potatoes. CT-B proteins from Vibrio cholera B toxin can be expressed in the leaves, stem, fruits, and other tissues.[27]

Carrots-

Carrots are not only nutritious and tasty, but they may also be used to make edible vaccines. When developed in transgenic carrots, vaccines against HIV, E. coli, and Helicobacter pylori indicate potential effects. Consuming this form of antigen-containing carrot consumable vaccination benefits people with impaired immune systems. [28,29]

Alfalfa-

Alfalfa is a plant that is used to make edible vaccine, primarily for veterinary usage. In 2005, hog pest virus glycoprotein E2 transgenic alfalfa was developed. Echinococcus ganulosus Eeg95-EgA31 was expressed in Alfalfa plants.[30]

IV. IDEAL PROPERTIES OF PLANT-BASED EDIBLE VACCINES- [31]

1. It should not be hazardous or pathogenic, i.e., it must be safe.
2. It should have a very low risk of adverse effects in healthy people.
3. It should not be problematic for people who have an impaired immune system.
4. It should produce humoral and cellular immunity that lasts a longer duration.
5. The immunisation procedure should be straightforward.
6. The vaccine should be more affordable.
7. There should be no environmental contamination.
8. It should be efficient and cost-effective.

V. CHALLENGES IN THE PRODUCTION OF PLANT-BASED EDIBLE VACCINES- [32]

Although many plant-based vaccines are still in phase 1 clinical studies, some vaccines have completed phases II and III trials. Insulin was produced in transgenic safflower (Sem Bio Sys), growth factor was produced in transgenic barley (ORF Genetics), taliglucerase alfa was produced in transgenic carrot (Protalix BioTherapeutics), avian influenza vaccine was produced in transgenic tobacco (Medicago), an Ebola vaccine was produced in transgenic tobacco (Medicago) (Mapp Biopharmaceutical). Nonetheless, no plant-based vaccination has been licenced for human consumption as of yet. It's worth noting that, even though plant-based vaccine production has been underway for nearly two decades, there are still a few obstacles to overcome.

1. Selection of Antigen and Plant Expression Host
2. Consistency of Dosage
3. Manufacturing of Vaccines according to GMP Procedures

VI. APPLICATIONS OF PLANT-BASED EDIBLE VACCINES-[33]

1. Malaria
2. Measles
3. Hepatitis
4. Autoimmune diseases
5. Diarrheal Diseases
6. Anthrax
7. Norwalk virus

VII. CONCLUSION

Edible vaccines made from plants are made by introducing desired genes into plants and driving the plants to generate the changed protein. Edible vaccines generated from plants may pave the way for a future of safer and more effective vaccination. From a review of the literature. It appears to be inexpensive, stable under a variety of settings and features a novel oral immunisation technique. Plant-based Edible Vaccines have effectively overcome the challenges of evolving vaccination technology. Even though global access to health care is limited and that complicated diseases such as HIV and malaria continue to receive a lot of attention,

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affordable, safer, and effective delivery mechanisms in the form of edible vaccines will be required in the future. There is a gleam of hope predicated on the assumption that most edible vaccines would be developed in developing nations This is essentially true, as they would be used in these countries. As a result, shortly, plant-based consumable vaccines will present a greater possibility. Although injectable needles are used, there may be a beneficial way available where an individual can be protected. By simply eating fruit, he is protected from sickness.

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