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FROM FARM TO IMMUNITY: THE PROMISE OF EDIBLE VACCINES

R. SUNITHA[1], V. TRIVENI[1], K. MANJEERA[1], K. ASHOK[1], K. BHUVANESWARI[1], S. BHUVANESWAR[1], G. RAJA KUMAR[1], T. ANIL KUMAR[1] AND S. GANESH[1]

1: A. M. Reddy Memorial College of Pharmacy, Petlurivari palem, Narasaraopet, A.P., Pin-522601, India,

***Corresponding Author: Dr. R. Sunitha: E Mail: raminenisunitha@gmail.com**

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ABSTRACT

Vaccines have been instrumental in curbing infectious diseases worldwide. However, the high costs and logistical hurdles of traditional injectable vaccines present major obstacles, especially in low-resource areas. Moreover, effective and affordable vaccines are still lacking for some diseases. This situation underscores the critical need for innovative immunization strategies. Traditional vaccine production and delivery methods are particularly constrained in remote and impoverished regions, leaving significant populations unvaccinated. Plant-based vaccine platforms, offering a more accessible and cost-effective approach, are being explored by scientists to tackle these challenges. Edible vaccines, created by genetically engineering plants to produce disease antigens, represent a promising alternative. This paper delves into the world of edible vaccines, examining their history, various types, benefits, drawbacks, potential future uses, and recent research. By harnessing the accessibility and low production costs of plants, edible vaccines offer the potential to transform immunization, particularly in resource-constrained environments.

Keywords: Vaccines, Immunization, Edible vaccines, Transgenic plants, infectious diseases

INTRODUCTION:

Vaccines are a cornerstone of infectious disease prevention. The advent of vaccines ranks among the most significant achievements of modern medicine. They have proven remarkably effective in preventing infectious diseases and have saved countless lives. Despite widespread childhood immunization efforts against six major diseases, 20% of infants remain unvaccinated. This lack of coverage contributes to approximately two million preventable deaths annually, particularly in remote and impoverished areas. Challenges in vaccine production, distribution, and delivery hinder universal access. Complete immunization coverage is crucial; unvaccinated populations can trigger outbreaks in areas with lower herd immunity that are otherwise protected. Furthermore, effective and affordable immunizations are lacking for some infectious diseases. DNA vaccines, while an alternative, face issues of cost and limited immune responses. Therefore, research is focusing on developing cost-effective, easily administered, stable, safe, and culturally acceptable vaccines and delivery methods. Inspired by Hippocrates' notion to "let thy food be thy medicine," scientists are exploring genetically engineering plants and plant viruses to produce vaccines against various ailments, including dental caries and life-threatening infections such as diarrhea and AIDS **[1]**.

Edible Vaccine Concept

The concept of edible vaccines emerged in the 1990s, pioneered by Arntzen. The first successful demonstration of an edible vaccine involved expressing a surface antigen from Streptococcus mutans in tobacco plants **[2]**. Edible vaccines are produced through genetic modification, where selected genes are introduced into plants, causing these genetically modified plants (GMP) to produce specific proteins. This "transformation" process results in "transgenic plants" **[3]**. These plants contain proteins derived from disease-causing pathogens. When consumed, the plant proteins are digested, and some of the protein is utilized by the body to build immunity **[4-8]**.

History of Edible Vaccine Development

Traditional vaccines, which are costly and require trained personnel for administration, are often inaccessible in developing countries, and are less effective in inducing mucosal immune responses. This inspired Hiatt in 1989 to investigate the production of plant-based antibodies for passive immunization. In 1990 **[5]**, the first edible vaccine was reported in a patent application, using tobacco to express a Streptococcus surface protein at a low level (0.02% of total leaf protein). Dr. Charles Arntzen pursued the concept of edible vaccines in 1997. In 1992, Arntzen and his team introduced the idea of using transgenic plants as a production and delivery system for subunit vaccines, with edible plant tissues containing the vaccine. This approach aimed to overcome the limitations of traditional vaccines, spurring research into the field **[9-14]**. During the 1990s, the Streptococcus mutans surface protein antigen A was initially expressed in tobacco. The same research groups also investigated Hepatitis B and the heat-labile toxin B subunit in tobacco and potato plants. In 1992, the successful expression of the Hepatitis B surface antigen (HBsAg) in tobacco was also accomplished. To prove that plant-derived HBsAg could be used for oral immunization, potato tubers were used as an expression platform and optimized to increase protein accumulation by 2000 **[15-19]**. Alongside HBsAg, Mason and Arntzen studied plant expression of other vaccine candidates such as the heat-labile toxin B subunit (LT-B) of Escherichia coli and the capsid protein of Norwalk virus. The plant-derived proteins were shown to assemble into functional structures capable of eliciting immune responses when fed to animals (1998) **[20-28]**.

Key Milestones in Edible Vaccine History:

- **1989:** Hiatt and colleagues first propose using plants to produce vaccines.
- **1990:** Dr. Charles Arntzen initiates the concept of edible vaccines by aiming to produce vaccines through the genetic modification of plants.
- **1990:** Hepatitis B surface antigen (HBsAg) is successfully produced in tobacco plants.
- **Mid-1990s:** The first patent for an edible vaccine is published involving the expression of a Streptococcus surface protein in tobacco.
- **Early 2000s:** Active development of edible vaccines for Hepatitis B and cholera are initiated.
- Ongoing efforts focused on refining the technology and assessing vaccine efficacy through clinical trials.

Mechanism of Action

Edible vaccines are developed using genetic engineering techniques such as **Agrobacterium-mediated transformation** and **gene gun technology**. The steps include **[30-39]**

1. **Gene Insertion:** A gene encoding an antigenic protein from a pathogen is inserted into a plant's genome.

2. **Expression & Accumulation:** The transgenic plant expresses the antigen within its edible tissues.
3. **Consumption & Immune Response:** Upon ingestion, the antigen is recognized by the immune system, activating mucosal immunity and systemic immune responses.
4. **Memory Formation:** Immune memory cells develop, offering long-term protection upon future exposure to the pathogen.

Types of Edible Vaccines

1. **Plant-Based Edible Vaccines:** These are produced using genetically modified plants such as bananas, potatoes, tomatoes, and rice, which express antigens that trigger an immune response upon consumption **[40-50]**.
2. **Fruit-Based Vaccines:** Certain fruits like papaya, strawberries, and grapes have been studied as potential vaccine carriers due to their palatability and high nutrient content **[11-60]**.
3. **Microbial Edible Vaccines:** Some probiotic bacteria, such as Lactobacillus and Saccharomyces cerevisiae (yeast), have been engineered to express vaccine antigens **[61-70]**.
4. **Genetically Engineered Edible Vaccines:** These vaccines involve advanced genetic modifications in plants and microorganisms to optimize antigen expression and stability **[71-73]**.

Applications of Edible Vaccines

Edible vaccines, produced in plants, offer a novel approach to disease prevention. Here are some areas where they show great promise:

Infectious Diseases

- **Hepatitis B:** Potatoes and bananas have been engineered to produce HBsAg.
- **Cholera:** Tomatoes and potatoes expressing cholera toxin B subunit.
- **Norovirus:** Plant-based vaccines against highly contagious gastroenteritis.
- **Rotavirus:** Edible vaccines targeting rotavirus infection in children.

Respiratory Diseases

- **Influenza:** Edible vaccines under research as an alternative to flu shots.
- **COVID-19:** Ongoing studies for plant-derived oral COVID-19 vaccines.

Veterinary & Zoonotic Diseases

- **Rabies:** Oral rabies vaccines for wildlife and domestic animals.

- **Foot-and-Mouth Disease:** Tobacco-based vaccines for livestock.

Cancer Prevention

- **HPV:** Research on edible vaccines to prevent cervical cancer.

Other Applications of Edible Vaccines:

- **Allergy Treatment:** Edible vaccines have the potential to help desensitize individuals to allergens, thereby minimizing allergic reactions.
- **Autoimmune Diseases:** Ongoing research is investigating how edible vaccines can modulate immune responses, offering promising therapeutic approaches for autoimmune conditions.

Advantages of Edible Vaccines

Edible vaccines have a number of potential benefits over traditional methods:

1. **Cost-Effective:** Lower production costs compared to traditional vaccines.
2. **Needle-Free Administration:** Eliminates risks of needle injuries and contamination.
3. **Easy Distribution:** No refrigeration required in many cases, aiding remote regions.
4. **Enhanced Mucosal Immunity:** Provides immune protection at pathogen entry sites.
5. **Eco-Friendly:** Reduces medical waste and dependency on cold-chain logistics.
6. **Culturally Acceptable:** Can be integrated into dietary habits for better compliance.

Challenges and Limitations

1. **Dosage Control:** Ensuring uniform antigen expression in plants is difficult.
2. **Stability Issues:** Environmental conditions may degrade antigen potency.
3. **Public Acceptance:** Concerns over genetically modified (GM) food must be addressed.
4. **Regulatory Barriers:** Approval processes for edible vaccines are complex and country-specific.
5. **Quality Control:** Ensuring batch-to-batch consistency remains a challenge.

Plant Species Used in Edible Vaccines:

Many plant species are being explored for edible vaccine production, each offering unique advantages. Here's a summary of some key examples:

- **Banana** – Used for oral vaccine production against diseases like Hepatitis B and rotavirus due to its palatability and ease of consumption **[74]**.

- **Potato & Tomato** – Commonly used in vaccine research for expressing antigens such as cholera toxin and Norovirus capsid proteins **[75, 76]**.
- **Rice** – A staple crop with potential for long-term vaccine storage and distribution without refrigeration **[77]**.
- **Lettuce** – A leafy green that can be consumed raw, making it suitable for oral vaccine delivery **[78]**.
- **Tobacco** – A model plant for vaccine research, though not edible directly; used for antigen expression and extraction **[79]**.
- **Carrot** – Engineered to produce vaccines for diseases like Hepatitis B and rabies **[80]**.
- **Maize** – High protein content makes it suitable for vaccine antigen expression and storage.
- **Alfalfa** – High biomass yield, making it useful for producing large quantities of vaccine material.
- **Soybean** – Used for producing plant-based antibodies and vaccine proteins **[81]**.
- **Spinach** – Studied for its potential in vaccine delivery against diseases like anthrax **[82]**.
- **Peas** – Rich in proteins and used as a medium for antigen expression.
- **Mushrooms** – Investigated for their high bioavailability in edible vaccine research **[83]**.
- **Barley** – A widely cultivated cereal with applications in oral vaccine delivery.
- **Chickpeas** – A high-protein legume studied for vaccine antigen production **[84]**.
- **Sweet Potatoes** – Rich in starch, which could serve as a carrier for vaccine proteins **[85]**.
- **Cucumber** – Studied for oral vaccine development due to its high water content **[86]**.
- **Papaya** – Engineered to express vaccines for diseases like Hepatitis B **[87]**.
- **Grapes** – A fruit with potential for vaccine delivery through juice-based applications.
- **Strawberries** – Investigated as a fruit-based oral vaccine carrier.
- **Watermelon** – Considered for large-scale antigen production due to high biomass.
- **Cassava** – A widely grown staple that could be genetically modified for vaccine production **[88]**.
- **Cabbage** – Explored as a leafy green for vaccine antigen expression.

- **Bell Peppers** – Rich in vitamins and being studied for potential edible vaccine production.
- **Pumpkin** – Considered for vaccine production due to its long shelf-life and high biomass.
- **Zucchini** – Examined as a potential edible vaccine delivery vehicle.
- **Apple** – Investigated for oral vaccine development due to its natural storage capabilities.
- **Orange** – Researched as a juice-based vaccine carrier.
- **Pineapple** – Explored for its enzymatic properties and potential in vaccine expression.
- **Dragon Fruit** – Studied for its potential in oral vaccine formulations.
- **Coconut** – Considered for vaccine delivery through its water and flesh.

Stability and Storage of Edible Vaccines

Stability:

- **Genetic Stability:** The inserted genes must remain stable throughout the plant's life cycle to ensure consistent antigen production.
- **Protein Stability:** The antigen proteins must retain their structure and function during plant growth, harvesting, and processing.
- **Environmental Factors:** Protection from environmental stressors such as temperature fluctuations, pests, and pathogens is crucial to maintain antigen integrity.

Storage:

- **Temperature Control:** Edible vaccines may require specific storage conditions; some may need refrigeration, while others can remain stable at room temperature.
- **Preservation Techniques:** Natural preservatives like salt or sugar can be used to extend the shelf life of edible vaccines.
- **Packaging:** Proper packaging is essential to protect vaccines from moisture, light, and contamination, ensuring their potency.

Scaling Up Edible Vaccine Production

1. **Genetic Engineering and Plant Selection**
   - **Optimizing Genetic Constructs:** Ensure that genetic modifications are stable and capable of producing high levels of the target antigen.
   - **Selecting Suitable Plant Species:** Choose plants that are easy to cultivate, have high

biomass production, and are commonly consumed, such as bananas, potatoes, and tomatoes.

2. **Cultivation and Harvesting**
   - **Large-Scale Cultivation:** Utilize greenhouse or open-field farming methods to grow genetically modified plants in bulk.
   - **Efficient Harvesting:** Develop optimized techniques to harvest the specific plant parts containing the vaccine antigens.
3. **Processing and Purification**
   - **Downstream Processing:** Implement methods to extract and purify antigen proteins while retaining their bioactivity.
   - **Quality Control:** Conduct rigorous testing to ensure the safety, efficacy, and consistency of the final vaccine product.
4. **Distribution and Storage**
   - **Protective Packaging:** Design packaging that prevents degradation during transport and storage.
   - **Cold Chain Alternatives:** Develop strategies to minimize refrigeration dependency, such as using natural stabilizers or freeze-drying techniques.
5. **Regulatory Approval and Public Acceptance**
   - **Compliance with Regulations:** Adhere to national and international guidelines to secure approval for edible vaccines.
   - **Public Awareness Campaigns:** Educate communities on the benefits, safety, and effectiveness of edible vaccines to encourage widespread acceptance.
6. **Economic Considerations**
   - **Cost-Effectiveness:** Streamline production to make edible vaccines affordable, especially for low-income regions.
   - **Market Demand Assessment:** Collaborate with governments, healthcare organizations, and industries to facilitate large-scale adoption and distribution.

Recently Developed Edible Vaccines:

Curd-Based Vaccines

Curd (yogurt) is being explored as a delivery system for edible vaccines due to its probiotic properties and wide global consumption. This approach, termed **"YoVac,"** utilizes lateral gene transfer (LGT) to introduce vaccine antigens into gut bacteria, stimulating antigen production in the digestive system **[89]**.

Applications of Curd-Based Vaccines:

- Tetanus (Tetanus toxoid)
- Diphtheria (Diphtheria toxoid)
- Pertussis (Pertussis toxoid)
- Hepatitis B
- Rotavirus infections
- Norovirus infections
- Influenza
- COVID-19 (ongoing research)

Bird's Nest-Based Vaccines

Traditional Chinese medicine (TCM) suggests that edible bird's nests offer medicinal properties. Research is investigating their potential for vaccine development due to their **wound healing, anti-inflammatory, and immune-boosting effects [90].**

Applications:

- Wound healing through tissue regeneration
- Potential anti-cancer properties
- Dietary supplements in capsule, powder, or beverage form
- Used in animal feed for nutrition enhancement

Poria Cocos-Based Vaccines

Poria cocos, a medicinal mushroom used in TCM, has immune-stimulating polysaccharides that make it a promising **immune booster or vaccine adjuvant.**

Method of Production:

1. Antigen gene insertion into Poria cocos genome
2. Controlled growth of mycelium
3. Formation of antigen-containing fruiting bodies
4. Processing into powder or capsules for oral administration

Applications:

- Influenza vaccine (H5N1 virus)
- HPV vaccine
- Hepatitis B vaccine
- Tuberculosis vaccine **[91]**

Red Hybrid Tilapia-Based Vaccines

Research is exploring genetically modified **Red Hybrid Tilapia (Oreochromis sp.)** as a delivery system for edible vaccines in fish and humans.

Applications:

- Edible vaccines for human diseases (Influenza, HIV, tuberculosis)
- Fish and animal health vaccines (Avian influenza, swine fever, bovine tuberculosis)

- Foodborne pathogen prevention (*Salmonella, E. coli*) **[92]**

Plant Oil-Based Vaccines

Plant oils like ***Camellia oleifera* and *Eucommia ulmoides*** are being studied as vaccine carriers.

Method of Production:

1. Extraction of plant oil from seeds
2. Emulsification with purified antigen
3. Formulation into an oral vaccine **[93]**

Applications:

- Human health: Influenza, HIV, tuberculosis vaccines
- Animal health: Avian influenza, swine fever, bovine tuberculosis vaccines
- Food safety: Pathogen prevention (*Salmonella, E. coli*)

Plant-Based Vaccines in Various Crops

Mushroom-Based Vaccines:

- Used for producing oral vaccines against **influenza, HIV, and tuberculosis**
- Engineered mushrooms act as a **bioreactor** for antigen production **[94]**

Spinach-Based Vaccines:

- Expresses **HIV and anthrax antigens**
- Genetically modified to produce **malaria and Hepatitis B vaccines [95]**

Strawberry-Based Vaccines:

- Can express **Hepatitis B surface antigen (HbsAg)**
- Investigated for **Norovirus and Rotavirus vaccines**

Barley-Based Vaccines:

- Engineered for **influenza, HIV, and tuberculosis vaccines**
- Studied for use in **animal disease prevention [96]**

Chickpea-Based Vaccines:

- Investigated for **Hepatitis B, cholera, and influenza vaccines [97]**

Apple-Based Vaccines:

- Engineered for oral delivery of **influenza, HIV, and tuberculosis vaccines**

Cucumber-Based Vaccines:

- Genetically modified for vaccines against **foodborne pathogens and human diseases [98]**

Cassava-Based Vaccines:

- Explored for **HIV, influenza, and tuberculosis vaccines [99]**

Algae-Based Vaccines:

- Engineered for vaccine production against **HIV and foodborne diseases**

Sweet Potato-Based Vaccines:

- Investigated for oral vaccines against **Hepatitis B, Rotavirus, and Norovirus [100]**

Dragon Fruit-Based Vaccines:

- Potential for edible vaccines against **infectious and foodborne diseases**

Alfalfa-Based Vaccines:

- High protein content makes it ideal for **oral vaccines**

Legume-Based Vaccines:

- Stable protein storage supports **animal and industrial vaccines**

Maize-Based Vaccines:

- Engineered for **Hepatitis B and rabies vaccines [101]**

CONCLUSION:

Edible vaccines are significant leap forward in immunization, offering a cost-effective, simple-to-administer solution with the added benefit of potentially triggering mucosal immunity. This makes them uniquely suited for resource – challenged areas. Though obstacles persist, current research and technological progress indicate that edible vaccines hold vast potential to revolutionize global health and propel us closer to eliminating infectious diseases.

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