AN ADVANCED EDITABLE COMPREHENSIVE REVIEW OF STRATEGIES FOR EDIBLE VACCINES

Niranjan Babu Mudduluru*[1], Sivagami Bojan[2], Haritha Baireddipalli[3]

[1]Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, A.P., India
[2]Department of Pharmaceutical Analysis, Seven Hills College of Pharmacy, Tirupati, A.P., India
[3]Department of Pharmaceutical Analysis, Seven Hills College of Pharmacy, Tirupati, A.P., India

Corresponding Author
Dr. M. Niranjan Babu
Professor Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, A.P., India – 517561, Contact: 7702484513, Email: principal.cq@jntua.ac.in

ABSTRACT:
An edible vaccine is a pharmaceutical product derived from antigens expressed in transgenic plants. This concept, introduced in the 1990s and developed by Dr. Charles Arntzen, represents a novel approach to oral immunization that has the potential to save millions of lives, particularly in countries where vaccination against infectious diseases is crucial. Edible vaccines function as preventive measures rather than treatments. They are cost-effective, easy to administer, and widely accepted as vaccine delivery systems, particularly beneficial for economically disadvantaged developing nations. It is estimated that edible vaccines may become mainstream medical products within 10-20 years. The future of this research hinges on public acceptance and willingness to use recombinant plants without fear.

KEYWORDS: Edible vaccine, Recombinant plant, Immune system, Transgenic plant.

INTRODUCTION:

Every year, over one million people succumb to infectious diseases, with 50% of these illnesses stemming from pathogens that infect mammalian mucosal membranes [1]. The current challenge lies in developing novel vaccines capable of targeting pathogens and infections at various stages. Vaccines, which enhance our immunity, were first proposed by Edward Jenner in 1796, starting with smallpox. Unlike traditional treatments initiated after disease onset, vaccination primes the body to combat future infections. It not only prepares us for future threats but also confers long-lasting immunity against those threats.

However, conventional vaccine production has been hindered by its industrial process, resulting in high costs that render them inaccessible to developing countries [2]. Edible vaccines offer a promising alternative as they are typically derived from antigen-expressing plants, requiring basic agricultural knowledge for production. Moreover, the purification and downstream processing steps, which contribute significantly to the expense of conventional vaccines, are eliminated in edible vaccine production [3]. Furthermore, post-translational

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modifications occurring in eukaryotic expression systems can enhance the immunogenicity of the expressed antigen [4].

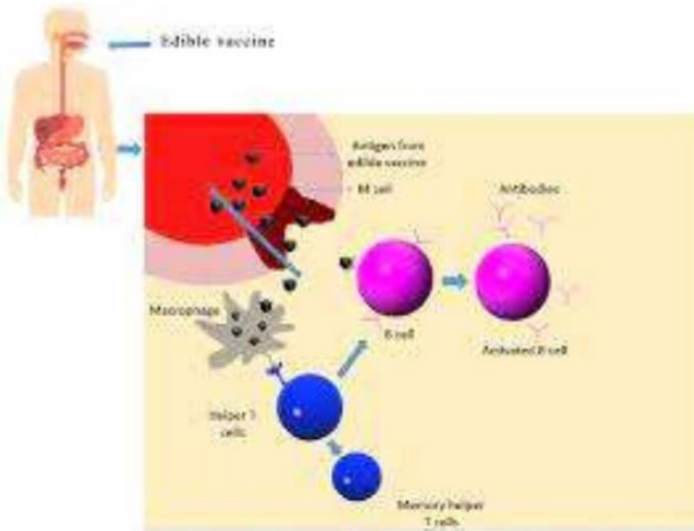
Historically, mammalian recombinant expression systems were used for such proteins despite being challenging to handle, expensive, and yielding low expression levels, thereby limiting their utility as protein expression platforms [5].

MECHANISM OF ACTION

Edible vaccines aim to activate the mucosal immune response system (MIS), which serves as the primary defense against pathogens initiating infections in humans. Mucosal surfaces line the digestive, respiratory, and urogenital tracts. Antigens can enter the gut mucosal layer through various mechanisms, including uptake by M cells and activation of macrophages by interferon gamma [6]. Activated macrophages present fragmented peptides to helper T cells, which in turn stimulate antibody production.

M cells provide another pathway for antigen transport to T cells. Antigenic epitopes are presented on the surface of antigen-presenting cells (APCs) with the assistance of helper T cells, triggering activation of B cells. Activated B cells migrate to mesenteric lymph nodes where they mature into plasma cells. These plasma cells then migrate to mucosal membranes, secreting immunoglobulin A (IgA). Secretory IgA (sIgA) forms in response to this process, which is transported into the lumen [7]. Production of sIgA involves B1 cells in the lamina propria and occurs independently of T cells. These sIgA are polyreactive and recognize foreign antigens, neutralizing invading pathogens in the lumen by binding to specific antigenic epitopes.

One of the most common challenges faced by oral vaccines/therapeutics is the development of tolerance in the gut. Various methods can overcome this issue.



CONCEPT OF EDIBLE VACCINE

Edible vaccines are developed by introducing a desired gene into a plant to produce the encoded protein. Typically, the coat protein of a non-pathogenic virus or bacterium is used for transformation. Various techniques are employed for transforming plants, algae, and bacteria into vaccine carriers. Edible vaccines offer scalability; for instance, the entire population of China could potentially be vaccinated using edible vaccines grown on just 40 hectares of land. The risk of contamination by plant pathogens is minimal, as these pathogens cannot infect humans.

Edible vaccines have been developed against diseases such as measles, cholera, foot and mouth disease, and hepatitis B, C, and E. Plants like banana, tobacco, and potato are commonly used as hosts for producing these vaccines.

In the late 1980s, the use of plants as recombinant expression systems started gaining attention. Compared to mammalian expression systems, plants offer significant advantages. They are powered by photosynthesis, which eliminates the need for external carbon supply. Additionally, the risk of pathogen contamination in plant systems is lower compared to mammalian systems, which is another notable advantage. These benefits make the production of antigens, vaccines, and other eukaryotic proteins particularly attractive in plants.

Edible algal vaccines resemble plant-based edible vaccines. Algae, often referred to as single-celled waterborne plants, include a limited number of strains that are considered edible for humans and can be genetically engineered to deliver antigens against various diseases. Using algae for vaccines offers several advantages Microalgae are easier to genetically modify, resulting in higher expression levels of foreign genes.

Algal vaccines tend to be more cost-effective compared to those produced by plants.
Algae serve as a potential food source for various species, including humans.

Microalgae are resistant to animal pathogens, making them well-suited for vaccine production.

PRODUCTION OF EDIBLE VACCINES

Antigens delivered into the body fall into two categories: proteins and peptides. The antigen can either be a full-length protein or a peptide fragment derived from a protein. The choice between using a protein or peptide antigen depends on specific circumstances. Two primary techniques utilize plant viruses to express immunogenic proteins or peptides in host plants: epitope presentation systems and polypeptide expression systems.

In epitope presentation systems, short antigenic peptides fused to the coat protein (CP) are presented on the surface of viral particles. Polypeptide expression systems involve the accumulation of unfused recombinant proteins within the plant. Edible vaccines are considered subunit vaccines as they contain proteins from a pathogen.

The initial steps in developing an edible vaccine include identifying, isolating, and characterizing a pathogenic antigen. For the antigen to be effective, it must elicit a strong and specific immune response. Once identified, the antigen's gene is cloned into a transfer vector. Agrobacterium tumefaciens is a commonly used DNA transfer vector for edible vaccines. The pathogen's sequence is inserted into the transfer DNA to produce the antigenic protein, which is then integrated into the genome and inherited in a Mendelian fashion. This results in the expression of the antigen in the fruit or plant. Subsequently, conventional vegetative methods and techniques are employed to cultivate the plants and propagate the genetic line.

LIMITATIONS AND CHALLENGES

While the concept of edible vaccination is promising, its practical implementation poses several challenges. Producing plant-based vaccines involves addressing numerous complexities, such as antigen selection, dosage determination, quality control, plant selection, delivery methods, efficacy, safety, public perception, and licensing.

Antigen selection is critical as it raises concerns about whether the chosen antigens can be safely expressed in the selected plant species. Factors like the weight, age, size, and ripeness of fruits or plants can influence the dosage. Variations in protein content among fruits (such as potatoes or bananas) of different sizes could potentially lead to underdosing, which may result in vaccine tolerance. Therefore, ensuring dose consistency from fruit to fruit, plant to plant, and generation to generation is essential.

Plant crops used for vaccines must also have a long shelf life to maintain efficacy and minimize the risk of spoilage. Another significant concern is preventing transgene escape and distinguishing vaccine fruits from regular fruits to prevent accidental vaccination misadministration. Methods used to increase antigenic protein concentrations in transgenic plants can introduce excess mRNA into the plant genome, potentially affecting plant growth and fruit production.

Furthermore, plant-based vaccines may pose risks of allergic reactions or other side effects such as cytokine-induced illness, central nervous system damage, or autoimmune diseases. Simplifying procedures without compromising quality is crucial for developing effective plant-based edible vaccines.

FUTURE PERSPECTIVES:

While edible vaccines are not yet available, advancements in agricultural and biotechnology fields make it conceivable that a child could one day be vaccinated while eating a tomato. The ability to transfer genes from one organism to a plant and express them in various plant parts—seeds, leaves, roots, or tubers—is now a viable concept. Food is increasingly recognized not only as a source of nutrition but also as a carrier of significant medical benefits.

Several factors will shape the future of edible vaccines. Public acceptance is crucial, necessitating widespread education on the use and advantages of edible vaccinations. The stability of genetically engineered plants is another critical milestone that must be achieved, requiring proper isolation of these plants.

Future research and development efforts on edible vaccines will focus on meeting WHO quality standards, including safety, potency, efficacy, and purity. If successful, these vaccines could potentially address numerous global diseases on a large scale.

DISCUSSION:

Edible vaccines offer significant advantages as a cost-effective, easy-to-administer, and culturally acceptable vaccine delivery system, particularly beneficial for economically disadvantaged countries. This approach involves integrating specific genes into plants to prompt them to produce targeted proteins. What was once a conceptual idea a decade ago has now become a reality, with a range of delivery systems developed and patents filed. Currently, edible vaccines are under development for both human and animal diseases.

The acceptance of genetically modified crops is on the rise globally, despite some resistance in certain regions. However, concerns regarding genetically modified foods could potentially impact the future adoption of edible vaccines. Despite these challenges, edible vaccines have overcome major obstacles on their path to becoming a viable vaccine technology. Various technical, regulatory, and non-scientific challenges have been addressed to advance this promising field.

The use of edible vaccines presents various advantages and disadvantages. Edible vaccines, in the form of fruits or vegetables, can be sold at an affordable price, unlike injectable vaccines such as those for diphtheria and tetanus, which are now inexpensive. Consequently, there may be less incentive to develop edible vaccines for these diseases. Injectable vaccines carry risks such as infections due to needle contamination, especially concerning in developing countries, which could potentially be minimized with edible vaccines.

However, one challenge of edible vaccines is controlling the dosage. It is crucial to determine the appropriate dosage to avoid inducing oral tolerance instead of an immune response against invading bacteria or viruses. Dosage requirements vary significantly based on factors like age, weight, fruit/plant size, ripeness, and protein content. For infants, oral vaccine intake is not convenient, suggesting that concentrating the vaccine in a small amount of baby food might be more practical than in whole fruits.

Edible vaccines primarily focus on disease prevention rather than treatment, leveraging the body's oral mucosa as the first line of defense against bacteria. While human experiments have shown promising results, the potential outcomes when exposed to actual viruses remain uncertain.

Another advantage of edible vaccines is the potential to combine multiple antigenic proteins by crossing plants that produce different vaccines. This combination effect could enhance vaccine effectiveness, which would be particularly beneficial in developing regions like Africa.

CONCLUSION:

Edible vaccines are pharmaceutical products produced by expressing antigens in transgenic plants. Introduced in the 1990s and pioneered by Dr. Charles Arntzen, this concept offers a convenient vaccine delivery system, particularly advantageous for developing countries due to the benefits of oral immunization. Unlike conventional vaccines, edible vaccines eliminate issues related to high costs, storage, and transportation. However, controlling the dosage of edible vaccines poses challenges in the absence of specific personal information such as weight or the ripeness/size of the fruit.

Currently, plant-based edible vaccines are under development for various human and animal diseases. Promising trials have been conducted, such as those for edible vaccines against hepatitis B, though their commercialization may still take time due to the need for further research. It is estimated that edible vaccines could become daily medical products within the next 10-20 years. The success of this research hinges on overcoming public apprehensions about using recombinant plants.

This innovative concept of oral immunization has the potential to save millions of lives, particularly in economically disadvantaged countries where vaccination against infectious diseases is crucial. Edible vaccines serve as preventive measures rather than curative treatments, harnessing the capabilities of genetically engineered plants to produce encoded antigens.

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