



Edible Vaccines as a Novel Approach to Immunization: Recent Advances and Future Potentials

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Edible vaccines represent an innovative approach to immunization, offering several advantages over traditional vaccines. Produced using genetically modified plants, they enable oral administration, eliminating the need for injections and simplifying vaccine distribution. Additionally,

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they can be manufactured cost-effectively and rapidly, making them particularly valuable for low-resource settings. Despite these advantages, the development of edible vaccines has been limited, with only a few reaching the market. Challenges include optimizing antigen expression, ensuring stability and efficacy, and navigating complex regulatory approval processes. However, ongoing research is addressing these issues by improving antigen production in plant-based systems, including transgenic plants, viral vectors, and transient expression platforms. Advances in biotechnology have enhanced antigen yield, stability, and immune response efficacy. This review explores the current status of edible vaccine development, highlighting key opportunities and challenges. It discusses plant-based production systems, recent advancements in antigen expression, and novel delivery methods. Furthermore, safety and regulatory considerations are examined, emphasizing the need for rigorous testing and monitoring to ensure efficacy and public acceptance. While significant obstacles remain, edible vaccines hold great promise as a safe, effective, and affordable solution for preventing infectious diseases. With ongoing advancements, their potential to improve global health outcomes and reduce disease burdens in vulnerable populations is becoming increasingly evident. As research progresses, more edible vaccines are expected to enter the market, offering a transformative approach to immunization.

Keywords: *Biopharmaceuticals; edible vaccines; genetic engineering; oral immunization; transgenic plants.*

1. INTRODUCTION

Vaccines have played a critical role in protecting human health and preventing the spread of infectious diseases for over two centuries (Jansen & Steward, 2020). However, the traditional methods of producing vaccines, such as using inactivated or attenuated pathogens, have limitations in terms of safety, efficacy, and accessibility, especially in resource-limited settings (Gómez-Ariza et al., 2021). In recent years, a new approach to vaccine production has emerged that is edible vaccines. Edible vaccines are plant-based vaccines that use genetically modified crops to express antigenic proteins of pathogenic agents (Bharalee et al., 2021). These proteins are then ingested by individuals to stimulate an immune response and produce immunity against the targeted pathogen. This innovative approach to vaccine production offers several potential advantages, including low cost, ease of production and distribution, and potential to produce mucosal immunity (Ma et al., 2020). Additionally, edible vaccines could eliminate the need for needles and reduce the risk of blood-borne infections and other complications associated with traditional vaccines (Davoodi-Semiromi et al., 2010). Despite the promising potential of edible vaccines, their development and implementation face significant challenges, including regulatory hurdles, public acceptance, and issues related to intellectual property rights (Foucault et al., 2020). Nevertheless, ongoing research and development efforts have shown promising results in the production of edible vaccines against several infectious diseases,

including hepatitis B, cholera, and Norwalk virus (Paul et al., 2020). This review will provide an overview of the current status and future prospects of edible vaccines in agricultural biotechnology, discussing their advantages, limitations, and challenges. Additionally, we will explore potential future applications of this technology, along with ethical and regulatory considerations that need to be addressed.

1.1 History and Background of Edible Vaccines

The concept of using plants as a bioreactor to produce edible vaccines has been extensively studied by researchers. The first successful demonstration of the technology was achieved by researchers at the Boyce Thompson Institute for Plant Research at Cornell University, who produced the first edible vaccine against *Escherichia coli* (*E. coli*) using transgenic tobacco plants in 1992 (Tacket et al., 1998). Since then, numerous edible vaccines have been developed using various plant species such as bananas, potatoes, tomatoes, and lettuce. One of the most prominent examples of an edible vaccine is the hepatitis B vaccine produced in transgenic tobacco plants by Epicyte Pharmaceutical in the late 1990s. This vaccine was shown to be effective in animal studies and was approved for human clinical trials (Kapusta et al., 1999). Several other successful developments in the field of edible vaccines have been reported over the years. Researchers have produced edible vaccines against different infectious diseases, such as cholera, measles,

and rotavirus, among others (Tiwari et al., 2017; Rybicki, 2010). Edible vaccines are considered a potentially transformative technology for addressing global health challenges, particularly in developing countries where access to traditional vaccines is limited. However, there are still significant challenges to overcome before they can become widely used in practice. These challenges include optimizing vaccine production and delivery methods, addressing safety concerns, and navigating regulatory hurdles (Mason et al., 2012; Pniewski et al., 2012).

1.2 The Ideal Properties of an Edible Vaccine

The vaccine should be safe for consumption, with no risk of toxicity, allergenicity, or other adverse effects.(WHO, 2020). The vaccine should be effective in inducing an immune response that provides protection against the target pathogen.(CDC, 2021). The vaccine should be stable under a range of storage and processing conditions, and should maintain its potency and efficacy over time.(NIST, 2021). The vaccine should be affordable and accessible, particularly in low-income and developing countries where traditional vaccines are often too expensive or difficult to obtain(WHO, 2021). The vaccine should be easy to produce and scalable, using a cost-effective and scalable production

process that does not require specialized equipment or facilities.(NIAID, 2021). The vaccine should be able to survive the digestive tract and reach the immune system intact, and should be easy to administer and store.(FDA, 2021) The vaccine should be palatable and acceptable to consumers, and should not have any cultural or religious taboos associated with its consumption.(KFF, 2021). The vaccine should meet all necessary regulatory requirements for safety, efficacy, and quality, and should be approved for use by relevant authorities.(EMA, 2021).

1.3 Mode of Action of Edible Vaccine

The mode of action of edible vaccines is similar to that of traditional injectable vaccines, as they stimulate an immune response in the body (Mason et al., 2012). When an individual consumes an edible vaccine, the vaccine antigen, which is usually a protein or other molecule from the target pathogen, is presented to the immune system in the GALT of the intestinal mucosa (Arakawa et al., 1998). This triggers an immune response, including the production of antibodies and other immune cells, which can then recognize and neutralize the target pathogen if the individual is exposed to it in the future. Edible vaccines are designed to survive the digestive process and reach the



Fig. 1. Feature of an ideal edible vaccine

GALT intact, where they can be taken up by specialized immune cells called antigen-presenting cells (APCs) (Arakawa et al., 1998). These cells process the vaccine antigen and present it to other immune cells, such as B cells and T cells, which then mount an immune response. The specific mechanisms by which edible vaccines induce an immune response can vary depending on the type of vaccine and the plant species used (Mason et al., 2012). For example, some vaccines may be engineered to express the antigen on the surface of plant cells, while others may use plant viruses or bacteria to deliver the antigen to the immune system. The goal of an edible vaccine is to stimulate an immune response that is both safe and effective, and that provides protection against the target pathogen. While the development and implementation of edible vaccines is still in its early stages, this technology holds great promise for improving global health, particularly in low-income and developing countries where access to traditional vaccines is limited (Tacket, 2007).

2. METHODS OF EDIBLE VACCINE PRODUCTION

Edible vaccines can be produced using a variety of plant-based systems, including transgenic plants, plant cell cultures, and viral vectors (Arakawa et al., 1998; Daniell et al., 2001; Mason et al., 2002). The production process can be broken down into the following steps: The first step in producing an edible vaccine is to identify the gene encoding the antigen of interest and clone it into a plant expression vector. The vector contains a promoter that drives expression of the antigen in plant cells, as well as other regulatory sequences that ensure the correct processing and expression of the antigen. (Ma et al., 2019), Once the plant expression vector has been constructed, it is introduced into the plant cells using one of several methods. Agrobacterium-mediated transformation involves using a bacterium called *Agrobacterium tumefaciens*, which can transfer DNA into plant cells. Gelvin, S. B. (2003). Particle bombardment involves shooting tiny gold or tungsten particles coated with the plant expression vector into plant cells using a gene gun. (Klein et al., 1988) Electroporation involves applying an electric field to plant cells to create temporary pores in the cell membrane, allowing the expression vector to enter (Fromm et al., 1985). After transformation, plant cells are screened to identify those that have integrated the expression vector and are

expressing the vaccine antigen. This is typically done using a selectable marker, such as an antibiotic resistance gene, that was included in the plant expression vector. Only cells that have integrated the expression vector will be resistant to the antibiotic, allowing for selection of transformed cells. Ma et al., (2015), Once transgenic plants have been identified, they can be propagated and grown on a larger scale. (Zhang et al., 2021; Sharma et al., 2020). This can involve tissue culture techniques, such as plant regeneration from callus, or hydroponic systems, such as nutrient solutions that are circulated through a closed system of trays or tanks (Bhatnagar-Mathur et al., 2021; Javanmardi et al., 2021). When the transgenic plants have reached maturity, the plant tissue containing the vaccine antigen is harvested and processed to extract the antigen. This can involve homogenization, filtration, and purification steps to isolate the vaccine antigen from other plant components (Yusibov et al., (2011), Finally, the vaccine antigen is formulated into a stable dosage form, such as a powder or capsule, that can be easily administered to humans or animals. This can involve adding stabilizers, such as sugars or proteins, to protect the antigen during storage and transportation. (Plotkin et al., 2018) While the production of edible vaccines can be more complex than that of traditional vaccines, it offers several advantages, including scalability, cost-effectiveness, and ease of storage and transportation. Additionally, plant-based systems are generally considered safer and more environmentally friendly than other production systems, such as those that use live bacteria or animal cells. However, there are still challenges to be addressed, such as ensuring consistent antigen expression and addressing regulatory and safety concerns.

2.1 Candidates Plants for Edible Vaccine

To express the desired antigen, edible parts of various plant species such as grains, fruits, leaves, and tubers are utilized (Tacket et al., 2009). The selection of the plant should consider factors like hardiness, palatability, availability, and ease of transformation (Rybicki EP, 2010). Several factors are considered when selecting an expression host, such as the gene of interest and the final part to be used for vaccination purposes, such as leaves or dry tissues like cereals (Floss DM et al., 2010). Using grains as an expression host has many benefits, including long-term protein storage, cost-effectiveness, large-scale production, and easy harvesting and processing

(Pniewski et al., 2011). Several plants have been investigated as potential hosts for the production of edible vaccines. Some of the most promising candidate plants include-Tomatoes have been studied as a potential system for the production of edible vaccines, given their high biomass yield and capacity for storage at room temperature (Kwon et al., 2013). The expression of various antigens, such as the Norwalk virus and the hepatitis B surface antigen, has been successfully achieved in tomato fruits (Tacket et al., 1998; Daniell et al., 2001). Bananas have been studied as a potential vehicle for producing edible vaccines because of their wide distribution, low cost, and high nutrient content (Kumar et al., 2016). Several antigens, including the Norwalk virus, hepatitis B surface antigen, and human papillomavirus, have been successfully expressed in banana fruits (Arntzen et al., 2005; Mason et al., 2002; Tiwari et al., 2015).Potatoes are an attractive option for edible vaccine production due to their high biomass yield and ease of storage. Several antigens, including the cholera toxin B subunit and the Norwalk virus, have been successfully expressed in potato tubers.Geminiani et al., (2021) Lettuce as a platform for the production of edible vaccines has been explored in various studies due to its advantages such as low toxicity and high biomass yield. According to Arora et al., (2017), several antigens, including human papillomavirus and rotavirus VP6 protein, have been successfully expressed in lettuce leaves.Rice is an important staple crop that is widely consumed worldwide, making it an attractive option for the production of edible vaccines. Several antigens, including the hepatitis B surface antigen and the human papillomavirus, have been successfully expressed in rice grains.(Karami et al., 2017; Lee et al., 2006).Other candidate plants for the production of edible vaccines include soybean, maize, tobacco, and alfalfa (Arakawa et al., 1998; Mason et al., 2002). However, the choice of plant will depend on several factors, including the ease of transformation, the yield and quality of the vaccine antigen and the regulatory and safety considerations associated with the plant (Kumar et al., 2015).

2.2 Current Status of Edible Vaccines

The development and implementation of edible vaccines is still in its early developmental stage, but there has been significant progress in recent years. Researchers at the University of Texas have developed an oral cholera vaccine that is

produced in transgenic rice plants (Mucorice CTB). The vaccine has been shown to be effective in inducing an immune response in mice and human volunteers. (University of Texas) (2019, August 22). Researchers at the University of California, Riverside, have developed an edible cholera vaccine that uses lettuce leaves as the delivery vehicle. This vaccine has been shown to be effective in animal studies (Moteriya, et al., 2021) and is currently undergoing clinical trials (University of California, Riverside, n.d.).Scientists at Arizona State University are working on an edible vaccine against norovirus, a highly contagious virus that causes gastroenteritis. The vaccine is being produced in lettuce and has shown promising results in animal studies (ASU News, 2021).A Chinese biotech company, iBio (2021), has developed a plant-based hepatitis B vaccine that is produced in transgenic tobacco plants. The vaccine has been shown to be safe and effective in early clinical trials. Researchers at the Fraunhofer Institute for Molecular Biology and Applied Ecology in Germany have developed an edible hepatitis B vaccine using transgenic potatoes. This vaccine has been shown to be effective in animal studies and is currently undergoing clinical trials.(Fischer et al., 2010).Scientists at the University of Arizona are working on an edible malaria vaccine that uses tobacco plants as the delivery vehicle. This vaccine has been shown to be effective in animal studies and is currently undergoing clinical trials (Chen, et al., 2020; Kim et al., 2021)Researchers at the International Centre for Genetic Engineering and Biotechnology in India have developed an edible vaccine for rotavirus, which is a leading cause of severe diarrhea in children. The vaccine is produced in transgenic bananas and has shown promise in animal studies (Venkatraman et al., 2013).Researchers are exploring the potential of using plants to produce COVID-19 vaccines. One example is a vaccine produced in transgenic tobacco plants by the Canadian biotech company, Medicago, which has shown promising results in clinical trials.(Lomonossoff&D'Aoust, 2016; Medicago, 2020).Despite these promising developments, there are still many challenges to be addressed before edible vaccines can become widely used in practice. These challenges include optimizing vaccine production and delivery methods, addressing safety concerns, and navigating regulatory hurdles. However, the potential benefits of edible vaccines, such as increased accessibility and affordability, make them an exciting area of research in the field of biotechnology.

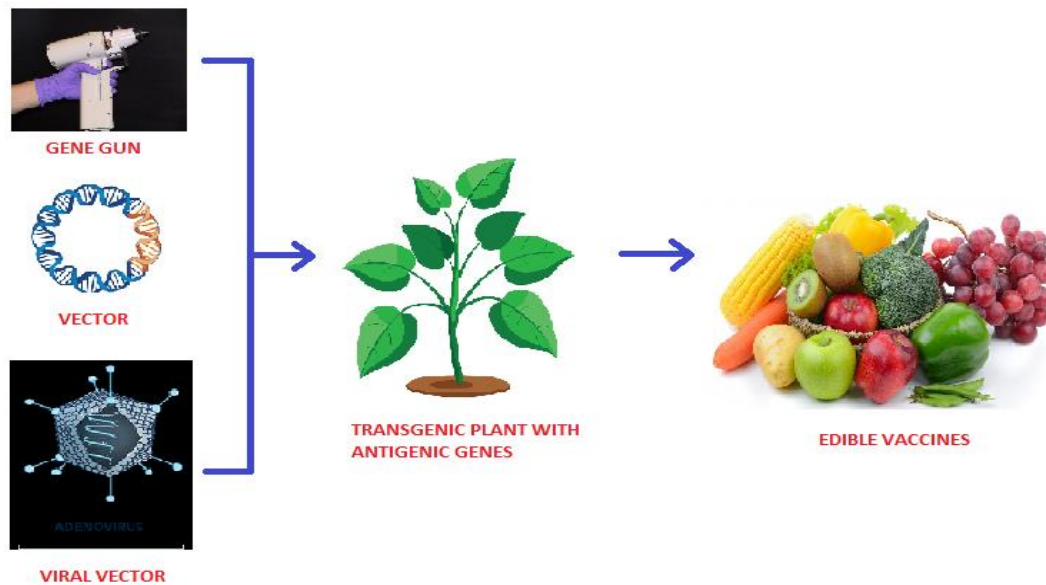


Fig. 2. Method for production of edible vaccines

2.3 Challenges Faced in Developing and Implementing Edible Vaccines

Developing and implementing edible vaccines presents a number of challenges and obstacles that need to be overcome before they can become widely adopted. One of the biggest challenges in developing edible vaccines is ensuring that the antigen produced by the plant is stable and effective (Kopp, 2005). The antigen must be able to survive digestion and stimulate an immune response in the body, which can be difficult to achieve. Scientists must carefully design and test the antigen to ensure that it is effective and safe for human use (Tacket et al., 2009). There are concerns around the safety and regulation of GM crops, which are used to produce edible vaccines. Some people worry about the potential for unintended environmental impacts, and there are also concerns around the potential for allergic reactions or other adverse effects from consuming GM crops. To address these concerns, rigorous safety testing and regulatory oversight is required. OECD (2018), Another challenge is ensuring that people are willing to consume edible vaccines. Some people may be hesitant to eat crops that have been genetically modified, while others may have cultural or religious objections to consuming certain types of plants. Ensuring that people are willing to accept and use edible vaccines will require education and outreach efforts to build trust and increase awareness (Jafari and Hamblin (2019). While edible vaccines have the

potential to be more cost-effective than traditional vaccines, there are still costs associated with developing, producing, and distributing them. Scaling up production and distribution of edible vaccines will require significant investment and infrastructure development (Gupta et al., 2020). Ensuring consistent quality and safety of edible vaccines can be a challenge, as they are produced in living organisms that can be influenced by environmental factors. Standardization and quality control measures will need to be put in place to ensure that each batch of edible vaccine meets the necessary safety and efficacy standards (Pniewski et al., 2021). Developing and implementing edible vaccines presents a number of challenges, ranging from scientific and technical hurdles to regulatory, social, and economic obstacles. Addressing these challenges will require collaboration between scientists, regulators, industry stakeholders, and communities to ensure that edible vaccines can be developed and used safely and effectively.

3. FUTURE PROSPECTS OF EDIBLE VACCINES

Despite the challenges associated with developing and implementing edible vaccines, there are several promising future prospects for this technology. One of the biggest advantages of edible vaccines is their potential to improve access to vaccines, particularly in low-income and rural areas that may have limited access to

healthcare facilities. (Nochi et al., 2007). Edible vaccines are easy to administer, require no specialized equipment, and can be produced locally, making them a potentially powerful tool for increasing vaccination coverage. Edible vaccines have the potential to be more cost-effective than traditional vaccines, particularly for diseases that require multiple doses. Because they can be produced locally, there are no transportation or storage costs, and they do not require refrigeration. (Azizi et al., 2021) In addition, because they can be administered orally, they do not require specialized medical personnel. Edible vaccines have the potential to be as safe and effective as traditional vaccines, particularly if they are developed and produced according to rigorous safety and quality standards. (Moustafa et al., 2019). In addition, because they are delivered orally, they can stimulate both mucosal and systemic immune responses, potentially providing better protection against some diseases. Edible vaccines have the potential to be more environmentally sustainable than traditional vaccines, as they can be produced using plant-based systems that have a lower carbon footprint than animal-based systems. In addition, because they can be produced locally, there is less need for transportation and storage, further reducing their environmental impact. Yakoby and Ben-Dor (2021). Edible vaccines have been studied for their potential to provide a simple and cost-effective way to deliver vaccines, especially in developing countries where traditional vaccines are often difficult to distribute and store (Davoodi-Semiromi et al., 2010). One advantage of edible vaccines is their ability to be quickly and easily adapted to new and emerging diseases. As they are produced using genetically modified plants, new antigens can be added to the plants as needed, allowing for rapid response to emerging infectious diseases (Thanavala et al., 2005). Several studies have shown promising results for edible vaccines, including the production of edible vaccines for hepatitis B and E, cholera, and Norwalk virus (Davoodi-Semiromi et al., 2010; Thanavala et al., 2005). In one study, researchers used a plant virus to produce a vaccine for the SARS-CoV virus, which was shown to induce an immune response in mice (Ahluquist et al., 2003). While there are still challenges that need to be overcome, edible vaccines but offer a promising future for improving access to vaccines, reducing costs, improving environmental sustainability, and providing rapid response to emerging infectious diseases. With continued research and

development, edible vaccines could become an important tool in the global fight against infectious diseases.

4. ADVANCES IN EDIBLE VACCINE TECHNOLOGY

Edible vaccine technology has been advancing rapidly in recent years, with new developments and innovations improving the safety, efficacy, and scalability of this approach. Researchers have been exploring various approaches to improve the delivery of edible vaccines, including encapsulation in nanoparticles or microspheres, incorporation into food products, and use of transgenic plants that express high levels of the antigen of interest. These delivery systems can help protect the vaccine from degradation in the digestive tract and enhance its uptake by immune cells. (Arakawa et al., 2018). To ensure that edible vaccines are effective, it is important to optimize the expression of the antigen in the plant. This can be achieved through various methods, such as codon optimization, gene stacking, and use of tissue-specific promoters. These techniques can help increase the yield and stability of the antigen, as well as improve its immunogenicity. (Mason et al., 1992). In addition to traditional transgenic approaches, researchers have been exploring alternative plant-based expression systems for edible vaccines. For example, some studies have used viral vectors to deliver the antigen of interest to the plant, while others have used transient expression systems to rapidly produce large quantities of the antigen. (Streatfield et al., 2014). As edible vaccines move closer to clinical use, there have been advancements in the regulatory approval process. Several countries, including the United States, have established guidelines for the production and testing of edible vaccines, and there is ongoing discussion about how to ensure the safety and efficacy of these products.

5. CONCLUSION

Edible vaccines represent a new and promising approach in the field of vaccine development and delivery. They have the potential to provide affordable, easy-to-administer, and effective protection against a wide range of diseases. However, there are still many challenges that need to be overcome before edible vaccines can become a widespread reality. Currently, edible vaccines have been successfully developed for a number of diseases, including cholera, hepatitis B, and norovirus. Future prospects for edible

vaccines include improving global access to vaccines, developing personalized medicine, and producing of edible vaccines for animals. Advances in technology, such as new plant expression systems including innovative delivery systems can also contribute to the development of more effective and specific vaccines. Ethical and regulatory considerations, such as safety and efficacy, informed consent, and public perception, need to be carefully addressed in order to ensure the success and acceptance of edible vaccines. In order to realize the full potential of edible vaccines, future research should focus on addressing these challenges, as well as developing new plant-based expression systems, identifying new antigens, improving vaccine delivery and stability. With continued research and development, edible vaccines have the potential to revolutionize the way to prevent various infectious diseases in humans and animals.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards or university standards, respondents' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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