Agri Articles
(e-Magazine for Agricultural Articles)
Volume: 05, Issue: 06 (NOV-DEC, 2025)
Available online at http://www.agriarticles.com
©Agri Articles, ISSN: 2582-9882

Molecular Farming for Immunization: Current Advances and Future Prospects in Plant-Produced Vaccines

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Plants are used as bioreactors in molecular farming to make vaccines, therapeutic proteins, and enzymes in a way that is both environmentally friendly and cost-effective. This approach offers high scalability, safety, and low contamination risk. Improvements in gene editing, temporary expression, and nanoparticle delivery have made it more effective. Medicago's Covifenz COVID-19 vaccine is an example of how quickly it can respond. Edible vaccines are a good option for areas with few resources because they don't need to be kept cold. But there are still problems to solve, such as low protein yield, complicated purification, and regulatory issues. This review talks about how plant-based vaccines have come along, how they can be used, and how they could be used in the future to make immunisation around the world more affordable and accessible.

Introduction

Global health challenges like COVID-19, influenza, and malaria have exposed the limits of traditional vaccines, which are costly, slow to produce, and difficult to distribute, especially in low- and middle-income countries. Molecular farming, which uses plants as bioreactors, offers a sustainable and affordable alternative for vaccine production. Plants can produce therapeutic proteins and antigens safely, without risk of human pathogen contamination, and at large scales with lower costs. Techniques such as transient expression using Agrobacterium tumefaciens enable rapid vaccine production, as shown by Medicago's Covifenz, the first approved plant-based COVID-19 vaccine. Edible vaccines in crops like lettuce and tomatoes also promise easy delivery without cold storage needs. With advancements in genetic engineering and biotechnology, plant-based vaccines have the potential to revolutionize global immunization by providing accessible, efficient, and eco-friendly solutions.

Historical Perspective on Plant-Based Vaccines

The concept of using plants as biofactories for therapeutic proteins emerged in the early 1990s with advances in molecular biology and genetic engineering. Early research focused on producing simple recombinant proteins like antibodies and enzymes in crops such as tobacco and potato. A major milestone came with the successful production of human growth hormone and hepatitis B surface antigen in transgenic plants, proving plants could produce functional vaccine components. This led to the idea of edible vaccines using crops like tomatoes and bananas for easy, low-cost immunization in developing regions.

The development of transient expression systems revolutionized molecular farming, allowing rapid and high-yield protein production without stable genetic modification. The use of Agrobacterium tumefaciens and plant viruses enabled fast vaccine development, demonstrated by Norwalk virus and influenza candidates. The most notable success was Medicago's Covifenz, a plant-derived COVID-19 vaccine using virus-like particles (VLPs), approved in 2022 by Health Canada.

Plant-based vaccines have also advanced in veterinary medicine, showing potential for diseases like Newcastle and porcine epidemic diarrhea. These milestones mark the evolution of molecular farming into a promising tool for sustainable, large-scale vaccine production.

Mechanisms of Molecular Farming

Plant Expression Systems

Plant expression systems are the foundation of molecular farming for producing recombinant proteins and vaccines. Two main approaches are used: transient expression and stable transformation. Transient expression, often achieved through Agrobacterium tumefaciens–mediated agroinfiltration or viral vectors like Potato Virus X (PVX), enables rapid protein production within days. This system is efficient, cost-effective, and ideal for responding quickly to pandemics. Stable transformation integrates the target gene permanently into the plant genome via nuclear or chloroplast transformation. Chloroplast transformation offers higher protein yields, genetic stability, and prevents gene escape through pollen. Though slower, it supports long-term and large-scale vaccine production.

Plant Hosts in Molecular Farming

Common plant hosts include tobacco, lettuce, tomato, and maize. Tobacco (Nicotiana benthamiana) is widely used for high-yield transient expression. Lettuce and tomato serve as models for edible vaccines, offering oral delivery without processing, while maize enables large-scale, stable production with natural encapsulation of proteins.

Comparison with Other Systems

Compared to microbial, fungal, and mammalian systems, plant-based expression offers human-like protein folding and glycosylation, lower production costs, and reduced contamination risks. Though protein yields are generally lower and expression slower, plants provide a safer, more sustainable, and scalable alternative for vaccine and therapeutic protein production.

Applications of Plant-Based Vaccines

Infectious Diseases

Molecular farming uses plants to produce vaccines and therapeutic proteins. Plants like Nicotiana benthamiana, lettuce, and maize are engineered to express vaccine antigens. This method is low-cost, scalable, and safer, with no risk of human pathogen contamination. A key example is the plant-based COVID-19 vaccine (Covifenz). Plant-made vaccines are being developed for influenza, hepatitis B, malaria, and cholera. However, challenges include low yield, purification difficulty, and regulatory delays.

Edible Vaccines

Edible vaccines—produced in crops like bananas, tomatoes, and lettuce—allow oral immunization without cold storage, ideal for low Plant-based vaccines have shown strong potential against major infectious diseases like COVID-19, influenza, hepatitis B, and malaria. Medicago’s Nicotiana benthamiana–derived Covifenz vaccine was a major success, producing virus-like particles (VLPs) mimicking the SARS-CoV-2 spike protein. Similar VLP-based vaccines for influenza and malaria have also shown high immunogenicity in trials. These vaccines are cost-effective, scalable, and safe, offering rapid production and reduced contamination risks compared to traditional methods. -resource settings. However, challenges include inconsistent antigen expression, dosage control, and protein stability during digestion. Techniques such as freeze-drying and encapsulation are being developed to improve stability and delivery.

Therapeutic Vaccines

Therapeutic plant-based vaccines aim to treat diseases like cancer, autoimmune disorders, and chronic infections. They express tumor-associated or viral antigens that stimulate targeted immune responses. Studies have shown promising results for cancers such as lymphoma and breast cancer, as well as chronic infections like HIV and tuberculosis.

Veterinary Applications
Plant-based vaccines are also valuable in animal health, preventing diseases such as Newcastle disease, rabies, and foot-and-mouth disease. They are safe, affordable, and suitable for mass production. By reducing zoonotic infections, they support the "One Health" approach linking human, animal, and environmental well-being.

Benefits of Plant-Based Vaccines
Cost-Effectiveness and Scalability
Plant-based vaccines are highly economical and scalable compared to traditional systems that rely on costly bioreactors. Plants like Nicotiana benthamiana and N. tabacum can be cultivated in fields or greenhouses, requiring minimal infrastructure and resources. Local cultivation reduces transportation costs and cold-chain dependence, while edible vaccines further cut costs by enabling oral delivery through food crops.
Rapid Response to Pandemics
Plants can be genetically modified quickly to produce new antigens, allowing rapid vaccine development during outbreaks. Unlike egg- or cell-based methods that take months, plant systems can generate vaccine candidates within weeks. Controlled indoor cultivation ensures consistent yields, biosafety, and year-round production, making them ideal for pandemic preparedness.
Safety and Low Contamination Risk
Because plants are not hosts for human pathogens, they eliminate the risk of contamination common in animal-based systems. They also avoid the use of animal-derived materials such as fetal bovine serum, reducing zoonotic risks and ethical concerns while ensuring cleaner production processes.
Environmental Sustainability
Plant-based production is energy-efficient and environmentally friendly. It consumes less water, produces minimal waste, and generates a smaller carbon footprint than conventional vaccine manufacturing. Localized production reduces transportation emissions, aligning with global sustainability goals.
Overall, plant-based vaccines combine affordability, safety, speed, and sustainability—making them a transformative solution for equitable and eco-friendly vaccine production

Challenges in Plant-Based Vaccine Development
Production Challenges
Low and inconsistent protein yields remain a major issue in plant-based vaccine development. Expression levels vary with plant species, environmental conditions, and transformation methods, making it difficult to standardize production. Unlike controlled mammalian cell systems, plants are affected by temperature, light, and soil quality. Moreover, overexpression of foreign proteins can disrupt plant metabolism, reducing both yield and plant health. Ongoing research focuses on optimizing expression vectors, promoters, and growth conditions to improve stability and output.
Downstream Processing
Purification of plant-derived vaccines is complex and expensive due to the presence of other plant compounds. Achieving consistent glycosylation and protein folding is difficult, which can affect vaccine quality and immune response. Standardizing purification and quality control remains a major bottleneck for large-scale production.
Regulatory Hurdles
Regulatory frameworks, designed for conventional vaccines, pose difficulties for plant-based products. Approval processes for genetically modified plants are lengthy and costly, with strict testing for environmental safety, allergenicity, and efficacy. This slows the market entry of plant-derived vaccines.
Public Acceptance
Public skepticism toward genetically modified organisms (GMOs) is another barrier. Misconceptions about safety and ethics often hinder acceptance of plant-based vaccines.

Greater public education, transparency, and awareness are needed to build trust and promote adoption.

Recent Innovations in Molecular Farming

Recent advances are transforming plant-based vaccine development, enhancing yield, safety, and delivery.

Gene Editing (CRISPR)

CRISPR-Cas9 allows precise modifications in plant genomes, optimizing traits for higher antigen yield, stability, and human-compatible glycosylation. It can remove unwanted traits, improve promoters, and accelerate plant modification, addressing key challenges in plant-based vaccine production.

Nanoparticle-Based Delivery

Nanoparticles, including lipids, polymers, and VLPs, protect vaccine antigens, enhance stability, and enable controlled release. They improve oral or mucosal delivery, making vaccines non-invasive and cost-effective. Encapsulating plant-derived antigens in nanoparticles can also support edible vaccines with better bioavailability.

Artificial Intelligence (AI)

AI optimizes plant vaccine production by analyzing genomic and environmental data to maximize antigen expression. Machine learning accelerates plant line selection, growth condition optimization, and prediction of safety risks, speeding up R&D and regulatory approval. These innovations—CRISPR, nanoparticles, and AI—together improve efficiency, consistency, safety, and delivery of plant-based vaccines, expanding the potential of molecular farming for rapid and scalable vaccine production.

Future Directions

Plant-based vaccines are poised for personalized medicine, producing patient-specific antigens for cancer or autoimmune therapies, combined with CRISPR and bioinformatics for cost-effective, scalable production. Nanoparticles can enhance stability and immune response, while synergy with mRNA or other platforms broadens applications. Beyond human vaccines, plant systems may serve in diagnostics and chronic disease immunotherapies. Their rapid, scalable production can address global health inequities and improve pandemic preparedness.

Conclusion

Plant-based expression systems offer a cost-effective, scalable, and versatile platform for producing both pharmaceutical and non-pharmaceutical proteins. While technical challenges have largely been addressed, regulatory barriers remain the main obstacle to widespread adoption, particularly for therapeutic proteins. With demonstrated production capabilities, economic feasibility, and ongoing technological advancements, plant-made biologics hold significant promise for the future of sustainable and efficient biomanufacturing worldwide.

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