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Edible vaccines: A new approach for oral immunization

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Abstract
Vaccines are biological substances that build protection against several infectious diseases. The edible vaccine is a new development that allows the introduction of desired genes into plants. These engineered plants give rise to encoded proteins thereby providing immunity against infections. In poor developing nations, there are few limitations for the use of conventional vaccines such as – the high cost of production & purification, the need for sophisticated devices for storage such as cold chains, and safety issues where consumable vaccines can overcome such barriers. They offer many advantages such as ease of manufacture, storage, cost- effectiveness, and better acceptability by people globally. Recently, efforts are being made to the development of a green vaccine against the novel coronavirus. This article explores the concept of edible vaccines, emphasizing the applications and their current status during the COVID19 pandemic.

Keywords: transgenic plants, edible vaccine, green vaccine, mucosal immunity, immunogenic response

Introduction
A vaccine is a biological preparation that provides active immunity to a particular infectious disease. It contains an agent resembling the disease-causing microorganism. Vaccines are made from either killed or live but weakened forms of that particular microbe. It is designed to stimulate active immunity against one or several diseases, acting as an antigen without inducing the disease [11].

In the backdrop of the growing world population, the bio-economy must be maintained to develop sustainable production of food, medicine, and other essential commodities [9]. Conventional vaccines, on the other hand, maybe effective but also have many considerations including efficacy, stability, cost, and safety [7].

There is an alternative approach to immunization that comes into the picture in the form of Edible Vaccine. The concept of the Edible Vaccine was first introduced by an American biologist Charles Arntzen IN 1990, who entertained the possibility of improving immunity through fruit consumption [9].

Edible Vaccine comes under the subunit type of vaccines. Plants are suitable candidates for recombinant expression systems where desired genes are transferred into the plant by the process of transformation giving rise to encoded proteins. These genetically engineered plants are called transgenic plants [4].

There might be thought of why the need of edible vaccine over a conventional system? Many infectious diseases require vaccination in the form of multiple antigens to maintain and produce immunity. Edible vaccines fit the requirement as they can express more than one transgene facilitating multiple inoculations. Conventional vaccines require sophisticated techniques and loads of research for their development and storage which might be a drawback for developing countries. Due to these reasons, there is an emerging need for the innovation of novel vaccine which solves cost-effectiveness and safety issues and edible vaccines looks promising in being an affordable, safe, and better acceptable vaccine delivery system.

Mechanism of action
Mucosal surfaces of the body are the most susceptible areas for infections to occur [5]. The mucosal immune response system (MIS) is the first line of defense that can be activated by oral vaccines against mucosal infections [3]. Edible vaccines are plant-based oral vaccines when ingested undergo mastication and degradation, a process of plant cells occurring in the intestine by the activity of digestive enzymes. IgA-producing plasma cells are abundant in Peyer's patches and have the ability to populate mucosal tissue and will serve as a mucosal

immune effector site. The edible vaccines break down near Peyer's patches which consist of 30-40 lymph nodules. It also contains follicles that form germinal centers for the activation of antigen- specific immunity. Penetration of vaccine antigens in the intestinal epithelium takes place through these lymphoid follicles. The vaccine's antigen is then taken up by a microfold cell (M cells). Microfold cells express class II MHC molecules and antigen transported across the mucous membranes by microfold cell activated B lymphocytes within the lymphoid follicles. The activated B lymphocytes migrate to mesenteric lymph nodes and differentiate into plasma cells thereby producing IgA antibodies in the lumen. These secretory IgA antibodies thereby neutralize the effect of the real pathogen**1**.

Advantages of edible vaccines [2]

- In comparison to needle-based vaccines, edible vaccines administration is safe and non- invasive.
- Edible vaccines are economical.
- They can induce mucosal immunity, which is not observed in conventional vaccines.
- Edible vaccines are comparatively easier to manufacture, store and transport, unlike conventional vaccines which need sophisticated techniques.
- Enhanced compliance can be seen with edible vaccines, especially in children.
- The need for trained personnel is meagre.

Limitations

- There are certain risks like

a. Development of immunity- tolerance to vaccine protein/ peptide.

b. The content of protein differs from plant to plant and generation to generation.

c. Uncertainty in the dosage of the vaccines from plant to plant.

- Stability issues exist with edible vaccines, whether they can withstand the harsh gastric environment in the human body.
- The selection of a suitable candidate for the edible vaccine is difficult.
- Certain edibles, such as potatoes cannot be eaten raw; when cooked, they result in denaturing the vaccine protein present in it.
- A major concern regarding edible vaccines is to identify distinguishing characteristics between an ordinary fruit and the vaccine-containing fruit to avoid mal-administration of edible vaccines leading to tolerance.

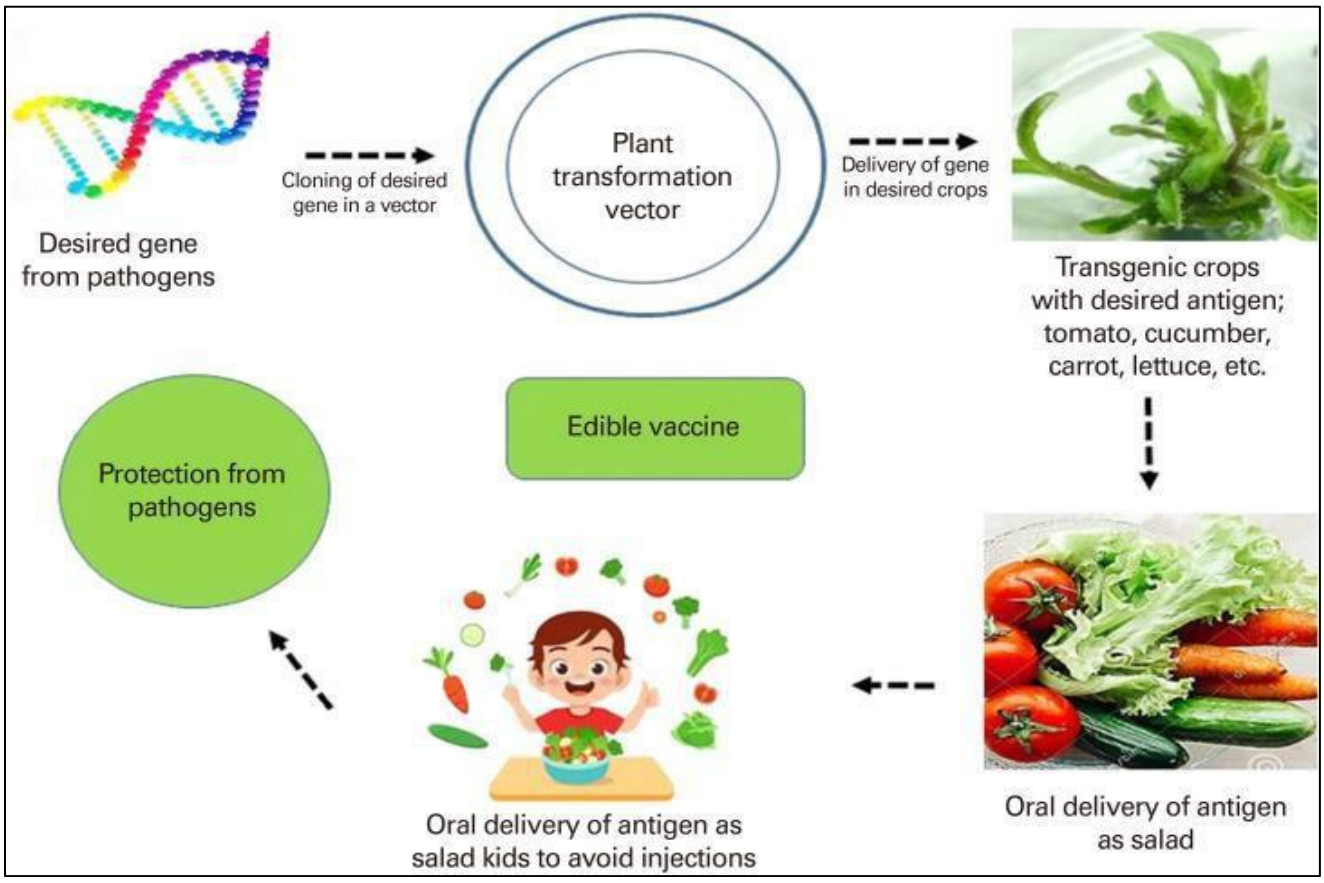

Fig 1: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7445323/#B5 13

Edible vaccines – as a plant source [1, 7]

Tomato

It is an ideal candidate for edible vaccines as it can be eaten raw and is immune to any thermal process thereby remaining stable. It is an appropriate candidate for the vaccine development for coronavirus. These plant-based oral vaccines when given to mice have shown a significant increase in SARS-Coronavirus-specific IgA antibody production.

Banana

Banana is a desired vector for vaccines. It has the advantage of being consumed in pure form. Studies are going on for the use of bananas as an edible vaccine. However, it has a disadvantage as it needs a long period to grow.

Tobacco

Though tobacco (Nicotiana tabacum) is not an edible plant, an attempt was made to produce an edible vaccine against acute watery diarrhoea by expressing heat-labile enterotoxin (LT-B) in tobacco

Carrot

Experiments have been done to develop an edible vaccine using a carrot. Studies have shown that carrot has a positive effect on the treatment of HIV. Carrot can be eaten raw and is healthful, thereby improving the immune system. Research in 2010 found that the UreB subunit of Helicobacter pylori in transgenic carrot can be a potential vaccine.

Rice

In 2007, it has been reported that transgenic rice (Oryza sativa) plants expressing the B subunit of Escherichia coli produce a significant number of antibodies against the subunit. India and China both being the two world's largest rice-producing countries have the capability to supply these vaccine plants all over the globe.

Current status of edible vaccines13

Product plant	Plant host	Indication	Product stage
Norwalk virus CP	Potato	Diarrhoea	Phase 1
HBsAg	Lettuce, potato	Hepatitis B	Phase 1
Rabies virus GP/NP	Spinach	Rabies	Phase 1
Anti-HBsAg scFV	Tobacco	Hepatitis B	On market
Gastric lipase	Maize	Cystic fibrosis, pancreatitis	Phase 2

Relevance of edible vaccines during COVID19 pandemic

COVID19 has been the biggest pandemic of modern times with millions of people affected. There have been many vaccines (administered by intramuscular route) developed for vaccination against the SARS-CoV-2 virus, including Covaxin, Covishield, and Sputnik V, etc. They can be deterred by various factors including price, maintenance, transport, and availability of medically trained personnel, especially in developing countries. Opposed to this, plant-based edible vaccines can be easily catered to the population on a global scale.

There is another cost-friendly alternative, which is plant-based VLP (virus-like particle). It is a multimeric protein that resembles the viral structure but does not have genetic material. By this technique, the target protein can be incorporated into the desired plant, which undergoes.

transformation mediated by agrobacterium. When ingested, the plant-based VLP triggers an immune response against the antigen [10].

Recently, a Canadian-based biotechnology company Medicago Inc. has moved on to phase III clinical trials for its plant-based vaccine against SARS-CoV-2 virus – CoVLP. The bacterium engineered with VLP is introduced in the Australian weed - *Nicotiana bethamiana*, which represents an ideal method of molecular farming. It is mediated by a single pandemic adjuvant, manufactured by GlaxoSmithKline (GSK). It has successfully advanced Preclinical, Phase I

& Phase II studies - with positive immunogenic responses [6]. To ensure the swift production of vaccines, a screening platform has been implemented by Medicago called VLP Express. It facilitates the testing of more than 200 different varieties of approaches for expression per week, resulting in Medicago's production rise consequentially [8].

Conclusion

The discovery of edible vaccines has been a notable outbreak in the field of Biotechnology. The scientists carried out many clinical trials and continue to do so, for plant-based edible vaccines against diseases like Swine Flu, Hepatitis B, etc. which could overcome some of the difficulties associated with conventional vaccines such as production, distribution, and delivery. Despite a few challenges, the perquisites of EV can be deemed reasonable enough to overcome its limitations. With the increasing number of diseases globally, edible vaccines could play a vital role in our efforts to prevent them.

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