Review Article

Edible Vaccine: A Novel Approach to Protect Against Different Physiological Disorders in Humans

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ABSTRACT

As prevention is often better and cheaper than a cure, scientists develop vaccines as a means of prevention, which are prepared from the etiologic agent and given to organisms to prevent future diseases. Around the world, vaccines are the most commonly used medical intervention. Vaccines lower death rates from a variety of infectious diseases. Using them has been considered among the safest and most effective approaches to treat a range of infectious diseases. The use of edible plants to vaccinate both humans and animals is a novel concept that holds considerable potential. It was first proposed as an idea around ten years ago, and it is now a reality. When an antigen is being expressed through the edible portion of the plant, it is known as an edible vaccine. Particularly for the poor developing nations, edible vaccines have enormous potential as an inexpensive, straightforward, failsafe, and socially acceptable vaccine delivery method. It involves introducing certain required genes into plants and then encouraging the production of an encoded protein by these modified plants. It was once believed to be helpful mainly in preventing infectious diseases. Still, it has now been used in the treatment of cancer, birth control, autoimmune disease prevention, and other areas. Currently, several human and animal illnesses are being studied for which edible vaccines are being developed. However, the main barrier to the widespread use of edible vaccines is public awareness, which necessitates educating the public about their advantages. Safer and more efficient vaccination will be possible if the main problems and limitations can be resolved. The Preparation process, mode of action, benefits and drawbacks, uses, and clinical trials regarding edible vaccines are reviewed in this paper.

Keywords: Edible vaccine, Mucosal immunity, Transgenic, Immunization, Transformation.

INTRODUCTION

Vaccine is actually a biological preparation designed to increase the production of antibodies, which results in immunity to a disease. Generally speaking, different vaccines are made from dead or attenuated organisms or purified substances obtained from them. Scientific developments in plant biotechnology, genetics, and molecular biology have enhanced our knowledge of several infectious illnesses and paved the way for the creation of immunization campaigns throughout the last ten years. Although injections are the most often used mode of vaccination administration, some are also administered via mouth or by way of nasal spray.[1]The effect of vaccinations on human health and lifespan is one of the most promising areas in scientific history. More than 300 years have passed since the initial discovery of the first vaccination.[2] Infectious disorders such as polio, measles, mumps, rubella, tetanus, and hepatitis were less likely to spread when immunisations were administered. Our immune system defends our body against the invasion of pathogens, which are bacteria that lead to disease. Infectious disorders will undoubtedly develop if our immune system is weakened and unable to combat the invasive microorganisms. Next is the important role of immunisation.[3] Administering vaccines is an affordable way to avoid the spread of illnesses and outbreaks. Therefore, the development of new vaccinations with financial and other advantages over current ones is essential. Using edible vaccinations is an alternative strategy that has offered fresh and profound hope for a better quality of life.

Edible vaccines are novel advances in plant biology and medical research that provide effective and affordable medications.[4] The proposal of edible immunisations was developed in the 1990s. Edible vaccines are made using rDNA technology, specifically Agrobacterium-based plant cell transformation. Commercial crops that trigger an immune response have been genetically modified to express the antigen are bananas, potatoes, rice, tomatoes, spinach, and others.[5]Vaccines made from plants are safer, offer the possibility of low-cost mass vaccination programs, and recommend increasing the use of vaccination for veterinary purposes. In the 1980s, new approaches to vaccine manufacture came about with the introduction of modern molecular biology technology. Proteins from pathogenic bacteria, viruses, or parasites make up these vaccines; typically, the protein is delivered by the expression of the protein-coding gene in a "surrogate organism" rather than pathogens themselves. [6]The process of creating edible vaccines involves introducing appropriate genes into the plant, then enabling the transformed plant to produce encoded proteins. The plants are "transgenic plants", and the process is "transformation". [7]Certain present barriers are removed when vaccinations are produced in plants. Considering that plants only need sunlight, water, and minerals, they are a cheap way to break down and express proteins, even complicated ones, properly. The formation of vaccines using plant tissues reduces the possibility of contamination with illnesses in animals, creates a heat-stable environment, and allows oral administration, which removes risks associated with injections.[8] The initial step towards producing an edible vaccine is choosing a proper vaccinogen. To drive genomic expression and identify the gene's terminus, an expression cassette is created by cloning the relevant gene that comprises plant regulatory sequences. The plant transformation process then makes use of this cassette.[9]Both gene-gun bombardment of embryonic suspension cell cultures, as well as more frequently, Agrobacterium tumefaciens, a naturally occurring soil-based bacterium that can enter plants through wounds (such as scratches), are methods for introducing foreign DNA into a plant's genome.[10]By using this approach, molecular scientists have been able to insert a desired gene into plant genomes using a plant expression cassette. T-DNA from the transgenic Agrobacterium is transferred into the host's genome by a process just likeconjugation when the bacterium is incubated with plant components. Transformed cells are regenerated into transgenic plants by positive selection during tissue culture. Regenerating a transgenic plant may take anything from six weeks to eighteen months, depending on the species.[11]Promoters that direct protein into the endoplasmic reticulum (ER) by combining ER-targeting and ER-retention signals, create an ideal translation start site context, and alter codons to accommodate the prokaryotic gene expressions in plants are additional techniques for expressing foreign genes in plants. It is preferable to use a plant whose components may be consumed uncooked to avoid deterioration while cooking and producing edible vaccines or antibodies. Tomatoes, bananas, and cucumbers are hence typically the preferred plants. [12]

METHODS

A thorough search for information on edible vaccinations was conducted to produce this evaluation. To ensure that the review included both publicly available and subscription-based papers, reliable sites like PubMed, ResearchGate, Google Scholar, and ScienceDirect were consulted. Terms such as "antigen expression in plants," "edible vaccines," "plant-based vaccines," "oral immunisation," "molecular farming," and "transgenic plants" were used in the search. To incorporate both the most recent research and earlier fundamental work, the search was made to encompass publications published between January 2000 and July 2025. A variety of publications, such as research articles, review papers, case studies, and clinical trial reports, were examined to provide a comprehensive understanding of the subject. To check citation information, the right journal and database records were used.

HISTORY

Due to the high cost, the necessity for trained medical personnel to administer, and the poor ability of traditional vaccines to generate a mucosal immune response, many individuals in underdeveloped nations lack access to the necessary vaccinations. Hiatt et al. (1989) were motivated by these demands to try to develop antibodies in plants that may be used for passive immunisation. [13] In 1990, the effective detection of antibody response in mice using Streptococcus surface protein antigen (SpaA) generated in tobacco plants marked a major milestone in the manufacturing of edible vaccines. A fourfold increase in intestinal antibodies following immunisation was demonstrated in the first human study, conducted in 1998 using modified potatoes carrying part of the diarrhoea-causing Escherichia coli toxin. [14] In 1996, it was shown that plant-derived hepatitis B surface antigen (HBsAg) may elicit mucosal immune responses when taken orally in potato tubers. [15]

A new chapter in vaccine delivery began in 1998 when scientists from the National Institute of Allergy and Infectious Diseases (NIAID) reported that an edible vaccine might induce notable immune responses in the human body for the first time. Researchers from Tulane University, the Boyce Thompson Institute for Plant Research, and the University of Maryland co-authored a study published in the May issue of *Nature Medicine*, that "Especially in the developing world, where storing and administering vaccines are often major problems, edible vaccines offer exciting possibilities for significantly decreasing the burden of diseases like hepatitis and diarrhea," declared the then-Director of NIAID. [16] Although research on edible vaccinations is still in its early stages, it has laid a preliminary basis that provides a framework for further development. There is still a long way to go before edible vaccines are incorporated into vaccination programs throughout the world. [17]

PRODUCTION OF EDIBLE VACCINE

One can generate edible vaccines by introducing a transgene within a specific plant cell. The transgene can be integrated using either the direct gene delivery strategy, which lacks the vector combination, or the indirect gene delivery method, which does. Two transformation systems can express the transgene in plants, depending on where the transgene should be incorporated into the cell (a transient transformation system and a stable transformation system).[18]

A. Direct Gene Delivery: It is a simple method. It involves the direct introduction of selected DNA or RNA into the plant cell.

1. Biolistic Method: A biolistic method, which is the most widely used direct gene delivery technology, is usually referred to as the gene gun or micro-projectile bombardment method. The method is independent of vectors. When gene transfer by Agrobacterium species-mediated transformation is not feasible, this is carried out. [19]It involves accelerating high-density, subcellular particles to a high velocity to transfer DNA and RNA into live cells. This method is flexible enough to be used for both the production of stable transformants and the research of transient expression.[20]The gene that contains DNA-coated metal (gold, tungsten) particles is shot into the plant cells using a gene gun. Such plant cells that pick up the DNA are then allowed to develop into new plants and are cloned to generate a large quantity of genetically identical crops.[21]But the gene gun approach commonly causes gene silence due to multi-copy and multi-site transgene insertions.[22]

2. Electroporation: Cell membrane structural rearrangement is known to occur when intense electric field pulses are applied to cells and tissue. Much progress has been made by embracing the theory that some of these rearrangements are made up of transient aqueous channels, or "pores," in which the electric field serves as both a local driving force for ionic and molecular transport through the pores and a cause of pore formation.[23]Transient holes in the plasma membrane are believed to be induced by introducing DNA into cells through a brief exposure to a high-voltage electrical shock. DNA must be able to penetrate the cell cytoplasm by weakening the cell wall, which acts as an efficient barrier, through moderate enzymatic treatment.[24]

B. Indirect Gene Delivery

The indirect gene delivery technique is vector-mediated, which produces the desired protein by attacking desired plant cells using plant bacteria or plant viruses. [25]

1. Agrobacterium-Based Gene Transfer: Utilising Agrobacterium tumefaciens, the first attempt to introduce heterologous genes into plants began in the early 1980s. Gram-negative A. tumefaciens is a soil bacterium that may change plant cells and introduce its own T-DNA. The bacterial genes that were inserted cause plant tumour tissues, like crown gall, to develop and encode plant hormones. Here, the bacteria use the Ti (tumour-inducing) plasmid to transfer genes.[26].It is possible to use the ability to introduce foreign DNA into the genome of plants. To prevent tumour formation, the plasmid must first be disarmed through the elimination of genes to produce auxin and cytokinin. In order to produce the desired product, which may be regenerated by itself, and to filter out the altered cells and plants that carry foreign genes, genes for antibiotic resistance are used[27].The method's slowness and poor yield are its drawbacks; it was particularly effective for dicotyledonous plants like tobacco, tomato, and potato, and studies have shown that the genes are expressed in experimental plants and animals using this method[28]. Vaccines for Diarrhoea, TB, dengue, avian flu virus, and Ebola can be produced by this method[29].

THE BENEFIT OF ADJUVANT TO THE EFFECTIVENESS OF EDIBLE VACCINE

Adjuvants can be added to some vaccines to enhance the induction of protective immunity, which is the purpose of vaccination. Ramon originally defined adjuvants as "substances used in combination with a specific antigen that produced a stronger immune response than the antigen alone." The word adjuvants came from a Latin word ‘adjuvare’, that means ‘to help or aid’[30].Nowadays, vaccination adjuvants includes oil-based emulsion and bacterial products such as CpG nucleotides, E. coli heat-labile enterotoxin B subunit, and V. cholerae toxin B subunit, VPLs (virus-like particles), saponin derivatives, liposomes, and synthetic adjuvants molecular. [31].Through enhancing innate immunity, encouraging antigen absorption, and enabling antigen-immune cell contact, these enhances the immunogenicity of edible vaccines. By using adjuvants to boost the immune response, inadequate antigen delivery may be lessened [32]. Combining antigens with such subunits can improve antigen absorption by M cells and alter immune responses associated with watery diarrhea. Applying a seed-specific expression system, researchers detected the expression of the cholera toxin B component linked to rabies glycoprotein antigen in peanut seeds. The transgenic seeds showed increased expression levels of the functional fusion protein, and further studies seek to ascertain whether these seeds provide effective defense against both rabies virus and V. cholerae [33].The encapsulating carrier vehicles reachs to the target immune-responsive locations and protect the edible vaccine complex from breaking down proteases.[34]

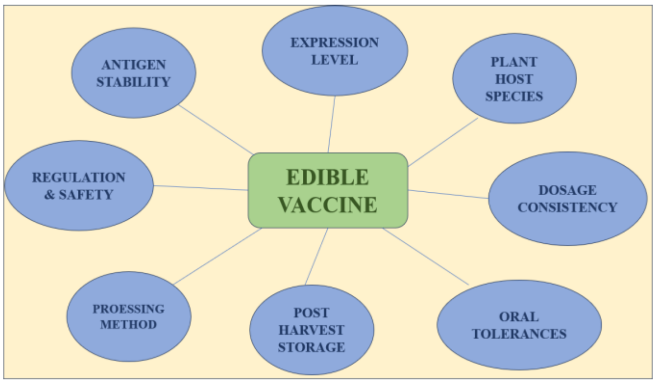

Figure 1: Factors affecting edible vaccine.

Table 1: Plant’s transformation procedure, microalgae, bacteria

Methods of transformation	Plant	Microalgae	Bacteria	Reference
Heat Shock Method			o	35
Agrobacterium mediated gene transfer	o	o		36
Biological method	o	o		37
Electroporation	o	o	o	38
Glass beads		o	o	39, 40

MECHANISM OF ACTION

Enhancing humoral and mucosal defences against infections is the aim of an oral vaccination. Since pathogens most commonly target mucosal surfaces, these are the most suitable targets for vaccination.[41].The most immunologically active tissues in the human body are mucosal epithelial tissues lining the gastrointestinal, respiratory, and urinary/reproductive systems; these tissues serve as the main entry routes for pathogens. First line of defence and an effective location for targeted immunisation against particular illnesses is the mucosal immune system (MIS).[42] T and B cells, which make up the innate and adaptive arms of mucosal immunity. The Mucosa-Associated Lymphoid Tissues (MALT) are the collective term for them. IgA can also help in protecting mucosal surfaces against toxicity and adhesion to microorganisms. To increase the efficiency of vaccines, new platforms are being developed to deliver the pathogens or toxin-specific IgA. Mucosa-Associated [43].When consuming edible vaccines orally, they are chewed, and the action of digestive enzymes in the colon breaks down the plant cells. Because Peyer's patches are a better source of plasma cells that generate IgA, they can colonise mucosal tissue to function as a mucosal immune effector site. During the administration of edible vaccines, M cells allow the antigen to enter tissues in the body at the site of action [44].In the intestinal section, microfold M) cells are a form of collecting antigens. A minor percentage of M cells contain enterocytes that are follicular-associated, or FAEs, that are widely distributed through digestive system. From the antigen-presenting cells (APCs) on Peyer's patches to the cavities in the colon, M-cells advantageously conquer a wide variety of protein molecules. In APCs, the main antigen-presenting cells are Dendritic cells [DC], causing the killer T cells to mount a flexible immune response. [45].The M cells promote transport across mucosal membranes, interact with antigens, express class II MHC molecules, and activate B cells inside lymphoid follicles. After emerging from lymphoid follicles, activated B cells from diffused mucosal-associated lymphoid tissue (MALT) convert to plasma cells, releasing IgA-class antibodies. [46].After that, IgA transforms into secretory IgA, which is subsequently transported across into the lumen. Secretory IgA production is a highly complex event, since B1 cells in the lamina propria create 50% secretory IgA (sIgA) in the gut lumen through a T-cell independent pathway. The foreign antigens are typically recognised by these poly-reactive sIgA. By reacting with the particular antigenic epitopes in the lumen, the invasive pathogens are neutralised by sIgA[47]

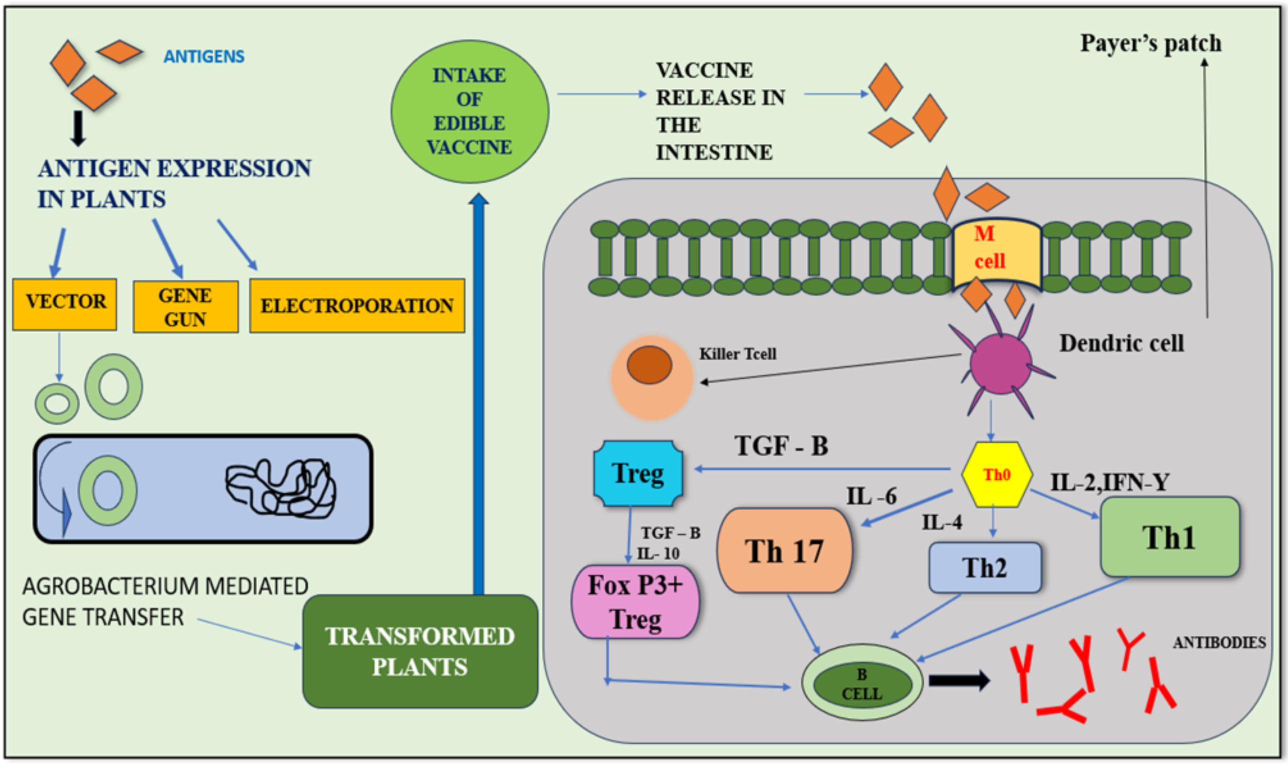

Figure 2: Production and Mode of action of edible vaccine.

SECOND GENERATION EDIBLE VACCINE

These are multi-component immunisations that offer defence against multiple infections that may generate multiple antigenic proteins[48].Since foreign genes have been effectively expressed in plant cells and/or edible parts, there is now a greater opportunity to investigate and increase the likelihood of creating plants that express multiple antigenic proteins [49].By crossing two rows of plants with different antigens, we may develop multi-component vaccinations. It is possible for the allergen of the same plant to co-express an adjuvant, an immunological component that enhances a vaccine's immune response.[50].The same plant may potentially co-express adjuvants along with the antigen. Vibrio cholerae toxin's B subunit (VC-B) tends to bind with its copies to form a five-membered, doughnut-shaped ring, creating a hole in the centre. These characteristics simultaneously deliver multiple antigens to M cells; for instance, a trivalent edible vaccine that protects against rotavirus, ETEC (Enterotoxigenic E. Coli), and cholera can effectively induce a synergistic immune response against all three enteric pathogens [51]

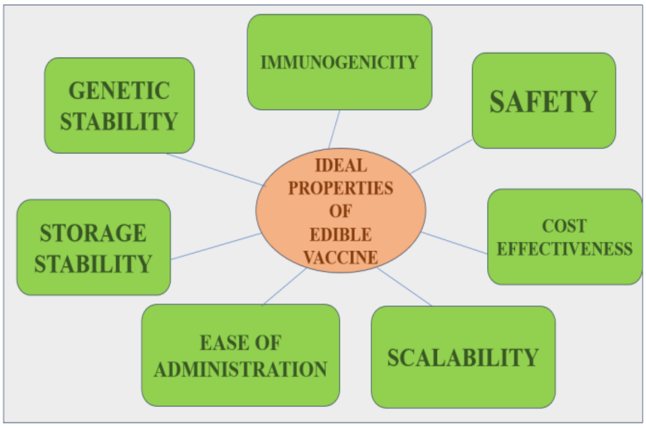

Figure 3: Ideal Properties of Edible Vaccine.

HOST PLANT CANDIDATE FOR EDIBLE VACCINE

Numerous plant species have been engineered to make vaccines up to this point. The selection of the plant species is crucial. A plant that is both edible and palatable is required if the vaccine is intended for raw consumption. When selecting a plant to serve as a vaccine for animals, it should be chosen from among those that are typically included in the animal's diet.[52].Various plants are employed, including cereals such as rice and maize, fruits like bananas, plant leafy tissues such as tobacco, alfalfa, and peanut leaves, and vegetable crops (potatoes, tomatoes, soybean seeds, peas, carrots, and lettuce).[53] Among these, bananas, tomatoes, carrots, peanuts, corn, and tobacco are the foods that are considered more promising for edible vaccines since these can be consumed raw. This is why these vegetable plants are widely accessible, and genetic engineering has effectively produced them[54]

Selecting plant species for vaccine administration:

The best plant to eat?

Capacity for unprocessed, raw consumption?

Suitable for babies?

Easy to store?

Able to withstand spoiling?

Can you be transformed and regenerated? [55]

The list of plants below includes edible vaccines that have been investigated in animals before and that need to be proven suitable for usage in humans and animals:

POTATO:

A staple of numerous foods worldwide, potatoes are a starchy root vegetable indigenous to the Americas. The perennial plant Solanum tuberosum, a member of the Solanaceae family of nightshade plants, is the source of potatoes.

The vaccine-based test developed using potatoes (i.e., Solanum tuberosum) to combat the LT-B strain caused by E. coli in mice was first carried out by Mason et al. In the same year, the antigens generated from potatoes (i.e., Solanum tuberosum) were found to be effective against the Norovirus capsid pathogen. The non-toxic part of Vibrio cholerae endotoxin in laboratory rats and human volunteers [56].The hypothesis put out by Thanavalas' group suggests that the potato may be used as an oral alternative to the injectable human hepatitis B vaccine [57].Benefits include ease, affordability, effectiveness, safety, and stimulation of antibodies.[58] One significant disadvantage is that boiling destroys the natural form of antigens; therefore, refrigerators are not required for storage[59,60]. The main mechanism by which edible potato vaccines function is by stimulating mucosal and systemic immune responses against a foreign infection.

TOBACCO:

Following the HBsAg expression in tobacco by Arntzen and others, the edible vaccination concept gained momentum. In 1990, tobacco was used to make the first edible vaccine, and it was discovered that 0.02 per cent of the total soluble leaf recombinant proteins, including a surface protein, was also discovered from Streptococcus. Under the International Patent Cooperation Treaty, a patent application was issued on how it first surfaced [61]. As a member of the family Solanaceae, tobacco refers to a group of plants with the scientific name Nicotiana, as well as any product made from their cooked leaves. Even though tobacco comes in more than 70 varieties, N. tabacum is the most significant commercial variation. The more potent N. rustica type is also utilised in several nations. Further in the year 1990, researchers modified tobacco against hepatitis B to develop edible vaccines, utilising the viral "s" gene as antigen after successfully generating the 0. [62].One notable achievement is a rabies vaccine that was created through the combination of tobacco seeds' cholera toxin B (CtxB) with the rabies G protein[63].Tobacco was used to create the Norovirus, which leads to gastrointestinal disorders. To avoid chickens with infectious anaemia, transgenic tobacco expresses the VP1 protein. Also, it is employed to develop a coccidiosis vaccine [64].In addition, human preclinical trials are already underway for antibodies against tooth caries that are expressed in tobacco. Finally, an affordable and immunologically potent vaccine against human papillomaviruses (HPV) has been developed by Italian researchers. HPV, the virus that causes skin, head, and neck cancers, can also cause cervical cancer.

Cervical cancer is one of the leading causes of mortality, associated with cancer. [65]

TOMATO

Another significant plant that is frequently utilised as an edible vaccination is the tomato. In 2007, Chowdhury and Bagasara proposed edible vaccines for anti-malaria, using multiple transgenic tomato plants expressing antigenic type(s). They postulated that vaccinating people against two to three antigens. And against every stage of the multistage life cycle of parasites would be a safe, effective, and inexpensive method of immunisation[66] Numerous illnesses, including septicemia, pneumonia, and vaccinations against the bubonic plague, have been identified in tomatoes.[67] The effectiveness of tomato-based vaccinations against or in favour of the virus is not higher than that of potato-based vaccines. Tomatoes were used to create the first effective vaccination against SARS.[68] It was the first plant to successfully create a vaccine against SARS, or coronavirus-induced acute respiratory illness. It has a greater effect on the Norwalk virus than vaccines composed of. The stem leaves, fruits, and other tissues have the ability to create CT-B proteins from Vibrio cholera B toxins. [69]It has a wider spectrum of customers because it tastes excellent and expands really quickly. The main drawback of tomatoes is their quick deterioration after ripening.[[70]].

BANANA

Bananas grow well in a tropical climate. This climate is present in the majority of third-world nations. Consequently, the majority of research is pointing to the use of bananas as an edible vaccine delivery system. [[71]]. Bananas are often liked by kids, and the plants thrive in tropical regions where immunisations are most required. Because many third-world nations, which stand to gain the greatest benefit from edible vaccinations, have tropical temperatures, research is thus moving toward using bananas as the vector.[[72]].Many people are aware that bananas are a common tropical plant that may be eaten raw or cooked. Interestingly, when heated, banana proteins do not break down, making them a viable option for the creation of an edible vaccination.[[73]]. Four different cassettes were used to report HBsAg expression in banana plants: PHER, PHB, pEFEHER, and pEFEHBS. Southern hybridisation, PCR, and reverse transcription PCR were used to examine the different stages of HbsAg expression. In banana leaves antigen was found, and the expression levels of the plant peaked at 19.92 ng/g. [74]. The reliable nature of bananas has risen as they are consumed raw and don't need to be cooked. It is also reasonably priced and a great source of vitamin A, which strengthens the immune system[75]. But the disadvantages are i. Trees take more than 2-3 years to mature. ii. Bananas are spoiled after ripening easily iii. It takes around a year for transformed trees to produce fruit[76].

RICE

Rice, a cereal grain, is the main source of nutrition in countries like Asia, Africa and 50% of the world's population. The grass species Oryza sativa, often known as Asian rice or, less frequently, O. glaberrima, referred to as African rice, is the source of rice[77]. A 2007 study demonstrated that the transgenic rice Oryza sativa produces a significant quantity of anti-E. coli antibodies. In 2008, HBsAg was functionally expressed in rice seeds. The general public's health will be greatly impacted by rice plant vaccinations in regions where rice is a key food source[78]. Rice seeds efficiently produced major T cell epitope peptides. These T cell epitope peptides are derived from Japanese cedar pollen allergens. To reduce allergic immune responses, these T cell epitope peptides were directed towards the mucosal immune system (MIS), especially to those linked to Th2 cells that are specific to allergens [79].Furthermore, rice plants have been altered to include the DNA of bacteria that produce cholera toxin. Rice grains fed to mice were protected against microorganisms that cause diarrhoea by the transgenic rice plants' effective synthesis of the toxin. This development shows how effective rice-based vaccines may be in preventing infectious diseases like cholera.[80],[81] Japanese scientists have developed a rice variety that can serve as a vaccination and keep for over a year and a half at room temperature. It grows slowly and needs certain glasshouse conditions, but it doesn't need needles, purification, or refrigeration.[82].Benefits over other plants included higher antigen expression in infant feeding and broad usage. But it requires both steady growth and glasshouse conditions[83]

MAIZE

One common plant used to make edible plant vaccines for both humans and animals is maize. The maize-based vaccination may work better if consumed as processed foods like tortillas, corn chips, or corn flakes. More than two billion people with hepatitis B might benefit from research being done at Iowa State University to create a way for humans and pigs to get flu shots by merely eating maize or items made from corn [[84],[85]]. Genetically modified maize may protect chickens against a very infectious and deadly viral illness that affects most avian species. The US business ProdiGene is genetically introducing a critical protein into maize. The protein was found on the surface of the monkey version of HIV. Maize is used as a vehicle for several edible vaccines [86] . It doesn't require cooling and is less expensive. The vaccination can be administered without the need for needles or a trained person. Their drawbacks are that they require cooking to use and take some time to arrive [87].

SPINACH

The concept of using genetically modified versions of spinach as a platform to create edible vaccines has been investigated in several areas of research [88]. Both HIV-1 Tat protein (a potential vaccine candidate) and anthrax vaccine are being experimented with as plant-derived, edible vehicles using spinach [[89],[90]]. In one experiment, spinach became infected with the recombinant virus after a translational fusion of a fragmented portion of protective antigen (PA), which comprises the majority of the receptor-binding domain, with a capsid protein on the surface of tobacco mosaic virus was expressed. In laboratory animals, plant-expressed PA is very immunogenic.[91]

LETTUCE

In the thermolabile protein, the B-subunit of Escherichia coli, that triggers enteric disease in humans and animals, is expressed by Lactuca sativa, suggesting that this vegetable may one day be used as an edible vaccine. In 2005, lettuce was discovered to express glycoprotein E2 of the common swine fever hog pest virus. The transgenic lettuce showing anti-hepatitis B virus properties is still in the developing stage in Poland [92,93].

SOYABEAN

Soybeans are a promising foundation for edible vaccines because of their high protein content. Cooked soybeans have 8.5 times the protein content of potatoes, which may result in greater therapeutic protein levels (0.085%).[94] Endoplasmic reticulum (ER) of soybeans (Glycine max) was applied to study the expression of the B-subunit of thermolabile toxin generated by the E. coli. This produced up to 2.4% of the total soybean seed protein as total antigen level, after drying for subsequent processing without any problem. In addition, rats given this protein orally have higher levels of systemic IgG and IgA[95]. To further suggest a possible immunological response, rats given these modified soybeans orally showed higher levels of systemic antibodies, such as IgG and IgA.[96]

Table 2: Merits and demerits of using different plants as edible vaccine

Plant/food	Advantages	Disadvantages	Reference
Potato	Spreading easily from its "eyes" Longer periods of storage without refrigeration whole complement of an antigen is not always eliminated when potatoes are cooked.	It needs to be cooked before eating. The antigen may become denatured by cooking.	97,98
Tobacco	A straightforward and efficient transformation technique; a wealth of information for characterizing proteins	Toxic alkaloids that cannot be administered orally; possibility of outcrossing in the field	99
Banana	Don't require cooking Low cost	The use of this vaccine was refused due to the shrub's lengthy growth time. Trees take more than 2-3 years to mature	100,101,102
Tomato	An edible vaccination that might prevent hepatitis B, Alzheimer's, anthrax, rabies, norovirus, and respiratory syncytial virus, SARS Rapid development, wide cultivation, and a high vitamin A concentration that could boost immunity	It spoils easily.	103
Rice	Benefits over other plants included higher antigen expression in infant feeding and broad usage. It doesn't need needles, purification, or refrigeration.	It grows slowly and needs certain glasshouse conditions	104
Lettuce	Grow quickly Consumption directly	Easily spoils	105
Soyabean	Huge crops, multiple times a year		106

APPLICATION OF EDIBLE VACCINE

1. AUTOIMMUNE DISEASES An effort was made to create plant-based diabetes vaccines using tobacco and potatoes that include insulin conjugated to the non-toxic B subunit of V. cholerae toxins to enhance M cell uptake of the antigens. This process can detect the cell protein that can enhance autoimmunity in those people who are suffering from Diabetes A. When transgenic potato and tobacco are given to non-obese diabetic mice, the IgG level is increased in the mice. IgG is an antibody linked to cytokines that inhibit detrimental immune responses. Therefore, in mice that acquire diabetes, vaccines can lessen the autoimmune attack and potentially delay the rise in blood sugar levels[107]

2. CANCER TREATMENT: Numerous plants are successfully modified for the production of monoclonal antibodies are excellent cancer-treatment drugs. The monoclonal body BR-96 functions efficiently in the soybean example as well. An agent that targets the medication doxorubicin, which leads to breast, ovarian, colon, and lung cancers[108]

3. GASTROINTESTINIAL DISEASE: The cholera vaccination can offer cross-protection against enterotoxigenic E. coli heat-labile enterotoxin (LT-B), as demonstrated by WHO research. When transgenic potatoes expressing LT-B were given to mice, it was found that they produced serum and secretory antibodies. As a result, the range of plants that might be utilised to make edible vaccines might be extended beyond raw food plants like fruits[109]

4. ANTHRAX VACCINE: Using a gene gun to infect tobacco leaves with the pag gene (Anthrax protection antigen, or PA) could trigger them to express a protein, which is structurally comparable to the main protein found in the current vaccine. It could be done to generate billions of units of anthrax antigen. In addition, this vaccination lacked the harmful and oedema factors that cause toxic side effects. Tomato plants have recently been exposed to the same anthrax antigen [110]

5. BIRTH CONTROL: ZB3 protein, which is produced when TMV is given to mice, is found in Mousezonapellucida and, due to the antibodies it produces, may stop mice's eggs from fertilising[111]

ADVANTAGES

1. Adjuvants, which stimulate the immune response, are not required for edible vaccines, resulting in an effective method of vaccination delivery.

2. Unlike standard vaccinations, edible vaccines can induce mucosal immunity.

3. Due to their plant-based production, edible vaccinations are widely accessible. Since any particular facilities, such as sterilisation, are needed to manufacture them, unlike typical vaccinations, production costs are affordable.[112]

4. Eating vaccines is relatively inexpensive since it doesn't require a cold chain as traditional shots do.

6. Because edible vaccinations are administered orally, they are frequently tolerated in contrast with conventional injectable vaccines. They reduce the need for certified medical personnel while decreasing the risk of contamination, as there is no need for buildings and manufacturing facilities to be cleansed.[113]

7. Compared to a regular vaccination, an edible vaccine increases individual safety since proteins cannot change into infectious organisms. Attenuated pathogens are not used in the production of edible vaccines, which are subunit preparations.

8. In contrast to an animal strategy, an edible vaccine may be produced in large quantities through breeding[114]

9. Efficient preservation of vaccine action by plant culture temperature management.[115]

10. Through oral administration, edible vaccinations lower the risk of infection and improve accessibility in isolated or impoverished regions by obviating the need for infrastructure, medical staff, and hygienic surroundings[116]

Edible vaccinations offer greater storage possibilities since transgenic plant seeds are easier to dry and have less moisture in them. In addition, plants with higher storage potential are those that generate oil or their aqueous extracts[117]

It is very simple to separate and sanctify vaccinations from production equipment, and dangerous contaminants from animal cells, which can be effectively.[118]

DISADVANTAGES

1. Immunotolerance to the protein of the vaccine or peptide might develop.[119]

2. Due to the requirement that some foods need to be cooked before eating, the immunostimulating qualities of the vaccine protein may be decreased or even eliminated.[120]

3. One of the main issues with edible vaccines is their variable conditions. Vaccine-containing potatoes should be kept at 45°F and may be kept for a longer period of time than tomatoes, which deteriorate quickly. Therefore, these vaccinations must be maintained correctly to prevent microbial deterioration and infection.[121]

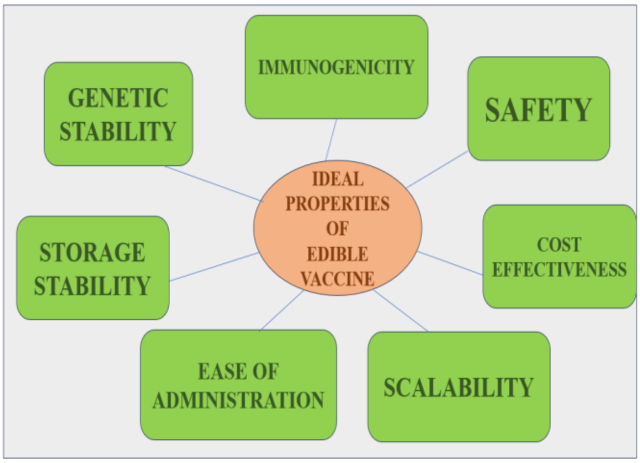

Figure 3: Ideal Properties of Edible Vaccine.

ROLL OF EDIBLE VACCINES IN DISEASES

1. **CHOLERA**

Vibrio cholerae is a comma-shaped bacterium that causes cholera, an illness that causes diarrhoea. It causes acute watery diarrhoea and enterotoxins like cholera toxin B (CTB) as it colonises the bowel[122]Every year, this illness affects about 10 million people, primarily in developing nations, with children being particularly at risk[123]Research has shown that transgenic mice carrying the V. cholerae CT-B gene are effective. When transgenic potatoes were given to mice once a week, for a month, with sporadic boosters, the work produced enhanced immunity. It has additionally been demonstrated that LT-B and mCT-A can be administered practically and successfully through the nasal route with agricultural seeds[124].

2. **DIABETES**

In India as well as throughout the world, diabetes is getting more and more prevalent. Diabetes harms over 100 million people globally. Type-I diabetes, often referred to as juvenile-onset diabetes or insulin-dependent diabetes mellitus (IDDM), typically affects children and young adults, which makes up 5–10% of all diabetes diagnoses in North America[125].In a study by a Canadian research team, non-overweight diabetic mice were given mutant tobacco and potato plants that had been bred with GAD67. These mice developed insulin-dependent diabetes on their own. The findings showed that, compared to 70% of untreated mice, only 20% of pre-diabetic animals that ingested transgenic plants developed diabetes[126,127].

3. **MALARIA**

The most severe parasite species, Plasmodium vivax and P. falciparum, are transmitted by infected female Anopheles mosquitoes and cause malaria[128].P. falciparum may develop over time and produce serious disease, which frequently results in death, if treatment is not received within 24 hours. Three antigens have recently been selected for the development of a malaria vaccine following extensive studies. Merozoite surface protein (MSP) 4 and 5 from Plasmodium falciparum and MSP4/5 from Plasmodium yoelii were the antigens derived from Plasmodium parasites. When cholera toxin B (CTB) was administered orally to mice as a supplemental treatment, recombinant MSP 4, MSP 4/5, and MSP1 induced antibody responses against the blood-stage parasite.[129].An anti-malarial edible vaccine in transgenic tomato plants was developed in order to address the logistical and transportation issues of getting immunised, which would be challenging to do given the present financial limitations[130]

4. MEASLES

In 2022, measles, a highly infectious viral respiratory disease that mainly impacts young children (under five years old), will primarily affect 800,000 persons worldwide, primarily in underdeveloped nations[131].Approximately 140,000 measles fatalities occurred worldwide in 2018, primarily in children under five, despite the development of a safe and affordable vaccination. Measles oral live attenuated vaccines have little oral effect and degrade when kept in a cold chain of refrigeration. The effectiveness is diminished because of the maternal antibody levels. Haemagglutinin (H) and fusion protein are the two surface proteins that are present; the H protein is infected by the wild-type measles virus [132].Mice fed tobacco that expressed MV-H (measles virus haemagglutinin from Edmonston strain) were shown to have secretory IgA in their stool and antibody titers five times higher than those thought to be protective for humans[133]

5. HIV

HIV affects our immune system, especially the CD4 cells, which belong to a subgroup of immune cells produced from T cells. HIV damages and ultimately kills CD4+ cells if treatment is not received. Acquired Immune Deficiency Syndrome (AIDS) is a degenerative illness that makes people more susceptible towards cancer and potentially fatal infections, brought on by this viral infection [134].A needle was used to effectively inject two HIV protein genes with CaMV as a promoter into tomatoes. And the generated protein was detectable by polymerase chain reaction (PCR) in several plant sections, including mature fruit, also in second-generation plants[[135],[136]].

6. FOOT AND MOUTH DISEASE

The picornavirus is responsible for foot and mouth disease. The illness is characterised by a high fever lasting from two to six days, followed by blisters on feets and inside the mouth[137].The infectious agent structural protein VP1 (viral protein) has epitopes that trigger the production of antibodies that neutralise the virus. This could appear as an immunogenic antigen in potatoes, alfalfa, and "Arabidopsis thaliana". These are employed for the production of an antibody response that is unique to and protective of viruses.[138]

Table 3: A Few Major Vaccines and Their Vehicle for Both People and Animals

SL NO	Vaccination against	Vehicles	Mode of administration	Approval status (USFDA/ FSSAI)	Clinical trial status	Reference
1	Human enterotoxigenic E. coli	Maize, Potato, and Tobacco	Oral	Not Approved	Early Phase I	139
2	Rabies	Tobacco	Intact glycoprotein	Not Approved	Early Phase I	140
3	Hepatitis B	Tobacco, Potato, Lettuce, maize, bananas	Oral	Approved (Existing vaccine)	Early Phase I	141,142
4	Insulin	Potato and Arabidopsis	Oral	Not Approved	No Clinical Trial Status	143
5	HIV	Tomato, Spinach, Arabidopsis, and tomato	Oral	Not Approved	No Clinical Trial Status	144,145
6	Gastroentritis	Maize	Oral	Not Approved	Phase I	146
7	Cholera	Potato	Oral	Not Approved	Phase I	147
8	Human measles	Tobacco	Oral	Approved (Existing vaccine)	No Clinical Trial Status	148
9	Human Norovirus	Potato and Tobacco	Oral (VLPS)	Not Approved	Early Phase I	149,150
10	Human SARS	Tomato, Milk	Oral	Not Approved	No Clinical Trial Status	151

CLINICAL STATUS

Numerous behavioural and biological investigations have been done to evaluate the potency, safety, effectiveness, and purity of edible vaccines. However, until enough data about the drug's safety can be obtained outside of the clinical environment, research investigations cannot start[152].The Food and Drug Administration thoroughly reviews laboratory and clinical testing for edible vaccines in order to collect data on their safety, efficiency, purity, and potency, just like it does for all other goods under its regulation. Only until adequate data regarding the level of the nonclinical safety have been gathered can these trials begin[153]. It has already been shown that plants may successfully express an antigen. A lot of animals are presently participating in research studies for different transgenic animal diets. The effectiveness of the vaccinations among humans has also been examined. For the first time, NIAID-supported researchers have shown that an edible vaccination may safely elicit strong immune responses in humans. Phase 1, named proof-of-concept trial investigation, aimed to show that a digestible vaccination might elicit a human immunological response[154].Although certain plant-derived vaccines have proceeded to advanced clinical testing, such as the Ebola virus vaccine, the World Health Organisation (WHO) has yet to approve any of them[155].

FUTURE

Since there are still some concerns about the potential uses of edible vaccines, much more study needs to be done in the future to guarantee their safety. The primary goal for these edible vaccinations is to be widely accepted because of the concerns expressed regarding the harm that these genetically modified items pose to society and the environment[156].If society accepts this, it will be possible to produce edible vaccines and vaccinate against a wide range of illnesses globally. Multiple gene expression in a single edible vaccine is one of the novel uses for edible vaccines, which might aid in the prevention of several illnesses with a single dosage or immunisation. This implies that ingesting one. An inoculated fruit or vegetable will shield you from a number of diseases. Furthermore, the future of edible vaccines will depend on how well certain WHO instructions are followed[157].It is necessary to take into consideration the ecological and environmental hazards associated with edible vaccinations. Before it is prepared for widespread testing in humans for the treatment of infectious illnesses and autoimmunity, it remains a highly undeveloped science[158].

Table 4: Some patents of edible vaccines

SL NO	Patent holder	Claim	References
1	Prodigene	Recombinant antigen production, delivery to plant cells using the plasmid-vector system	159
2	Ribozyme-Pharmaceuticals, Inc.	Plant, animal, or bacterial viral infections can be treated or prevented by nucleic acid vaccines.	160
3	Biosource	Cytotoxic T lymphocyte (CTL) and malaria B-cell production in plants as a result of viral coat protein fusion.	161
4	Institute Pasteur	Attenuated E. Coli vaccines are used in gene therapy.	162
5	Edible Vaccine, Inc.	An edible vaccination that uses its surface antigen to cure viral infections like hepatitis B	163
7	University Loma Linda	Edible vaccines made from gene structures are intended to cure autoimmune conditions, including diabetes and multiple sclerosis	164
8	University of Yale	Anti-invertebrate vaccine	165

DISCUSSION

The finding of an edible vaccine represents a significant breakthrough in biotechnology. Its success hinges on broad acceptance and attention. In comparison with the traditional vaccines, for vaccine production, there is no need for sophisticated equipment and machinery for the production of edible vaccines[166]. A vaccine made from edible plants could lead the way for more effective and secure vaccinations in the future. They might be included in vaccination schedules and would solve some of the issues associated with traditional vaccines, such as manufacturing, delivery, and distribution[167] Although manufacturing and investment in this new technology are still lacking, it is likely to overcome these challenges to increase the efficacy and reliability of plant-derived vaccines[168].To ensure stability, during post-harvest storage, the requirement to maximise expression levels is one of the many issues that have arisen since the first human clinical trials for plant-based vaccines. There is still uncertainty regarding the long-term consequences of edible vaccinations, particularly the potential for unidentified delayed reactions. In addition, adding a particular adjuvant, either fused with the candidate gene or given separately, can enhance the immunogenicity of oral edible vaccines [169].Despite the difficulties in creating and deploying edible vaccines, this technology has a number of bright future prospects. One of the main benefits of edible vaccines is that they may increase vaccine accessibility, especially in rural and low-income areas where access to medical services may be restricted[170].Because there are possibilities of cross-contamination during pollination between genetically modified and non-genetically modified plants in molecular farming, careful observation is necessary while cultivating plants for edible vaccine manufacturing. Unintentional pharmaceutical entrance into the human food chain is a possibility, and it might also have an impact on animals. A safe and efficient immunisation technique, edible vaccines can generate complex multimeric proteins that are not produced by microbial systems. In this area, proper research and development are necessary because the advantages of edible vaccines outweigh their drawbacks and have the potential to user to a new era of improved control over infectious diseases[171]. Recent years have seen an enormous development in edible vaccination technology, with novel discoveries and developments enhancing the approach's scalability, safety, and efficiency. Researchers have been investigating a number of techniques to enhance the delivery of edible vaccines, such as using transgenic plants that express high levels of the target antigen, encapsulating them in nanoparticles or microspheres, and incorporating them into food products. These delivery methods can improve the vaccine's absorption by immune cells and shield it against deterioration in the digestive system [172]. Several countries, including the United States, have established guidelines in production and testing for edible vaccines, and there are ongoing discussions about how to ensure the safety and efficacy of these products[173].

CONCLUSION

From this study, it is concluded that edible vaccines play a dual role by protecting mammals from different types of communicable and non-communicable disorders, which may be an artificial defence line in the human body in the future.

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Arnab Kumar Ghosh: Conceptualisation, Supervision, Resources, writing review and editing, Project Administration, Priyasmita Dey: Writing original draft, Investigation, Data collection, Abhijit Ghosh: Writing Original Draft, data collection and visualisation

ABBEVIATIONS

rDNA: Recombinant DNA Technology

ER: Endoplasmic Reticulum

SpaA: Surface Protein Antigen

NIAID: National Institute of Allergy and Infectious Disease

Ti: Timur Inducing

VPLs: Virus-like Particle

TB: Tuberculosis

MIS: Mucosal Immune System

MALT: Mucosa-Associated Lymphoid Tissue

FAEs: Folicular Associated Enterocytes

DC: Dendritic cells

HPV: Human Papillomavirus

GALT: Gut-associated lymphoid tissue

IgA: Immunoglobulin A

IgE: Immunoglobulin E

IgG: Immunoglobulin G

APC: Antigen Presenting Cell

WHO: World Health Organisation

TMV: Tobacco Mosaic Virus

E.coli: Escherichia coli

HIV: Human Immunodeficiency Virus

T-DNA: Transfer DNA

IDDM: Insulin-Dependent Diabetes Mellitus

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