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Review Article

A Comprehensive Review on Edible Vaccine

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Abstract

A New approach for vaccine delivery Antigen is the use of inexpensive of oral vaccines. Is ideal for edible vaccination since it grows quickly and has a lot of nutrients that improve the immune system. Edible oral vaccines supply exciting Prospects for considerably reducing the burden of disease like hepatitis and diarrhea Significantly within the developing world wherever storing and Administering vaccines are typically major problem. They have several benefits as they trigger the Immunity at the tissue layer surface which is the body's first line of defense. Painful vaccination processes are replaced by an edible vaccine. In comparison to traditional vaccines, edible vaccines are needle-free, low-cost, do not require refrigeration, may be stored close to the point of application, are safe, and give mucosal and systemic protection. Vaccines play a vital role in the prevention and treatment of a wide range of diseases. The Review's major goal is to provide comprehensive information on edible vaccines. The main aim of the Review is to provide an all over information related to edible vaccine. The hope is the edible vaccine could be grown in the developing Many of countries Where their need is more.

Keywords: (edible vaccine, fruits, immunity, vaccination, transgene, antigen)

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1. Introduction:

Immunization protects against preventable morbidity and mortality in a direct and effective manner. Jenner in 1796 had done one of most effective health interventions which Inoculation of cowpox virus in humans was successfully tested to prevent small pox in humans. The vaccine's composition is an agent that contains disease-causing microorganisms in weakened or dead form.[1]

Edible vaccine is nothing but transgenic plant and more over it trigger an animal's immune response. In general definition of edible vaccines are natural antigen prepared in plant or animal made pharmaceuticals. [2] This article gives highlights on the importance of edible vaccines produced in plants. Edible vaccine technique should be incorporated in prevention of first line defence against pathogens attacking via mucosa, like mycobacterium tuberculosis, HIV, diarrhoea, STDs, heart diseases. [3,4]

In developing countries, more oral vaccine accessible and affordable. The "edible vaccines" concept was created by Charles J Arntzen, who came up with the notion of employing edible plant components as factories for synthesizing vaccinations.[5] Ratio given by WHO globally more than 20 million deaths annually caused by various diseases.[6]

Vaccine play a vital role in controlling multifarious disease. They are classified into two form oral and injectable.[7,8] Now Advances in genetic engineering resulted in the development of recombinant subunit. Recombinant subunit vaccines more preferable than traditional products.[9] The ability to recombinant protein in desired from and function is one of the ability of plant.[10] For example, expression of human growth hormone in first transgenic tobacco was developed.[11]

Recently multiple plant species including Apple, Arabidopsis, Banana, Beans, Canola, Carrot, Clover, Lettuce, Maize, Papaya, Potato, Peanut, Rice, Spinach, Tobacco and Tomato contain edible vaccine.[12]

Along with advantages some limitations are also there for these vaccines. Several pathogenic agents can't be incorporated in plants due to highly pathogenic nature. Another negative factor chances of revert for attenuated bacteria into original form. Furthermore, almost all commercial vaccinations have strict expiration dates and refrigeration restrictions, which necessitate regular monitoring of the pathogen they contain, raising control, storage, and distribution costs. [12-15]

The goal of this review is to present comprehensive information on edible vaccines and to assess their potential as actual functional foods for the treatment of pathogenic diseases. This article includes overview about the several varieties of edible vaccines, how they'll be developed and evaluated, their benefits and drawbacks, the challenges they'll face as producers, their future possibilities, and everything else.

2. Types of Vaccine:

Mainly types of vaccine

A. Live attenuated (LAV): Tuberculosis, Oral polio vaccine, Measles, Rota virus, yellow Fever

B. Inactivated (killed antigen): Whole cell pertussis, inactivated polio virus, Hepatitis A

C. Subunit (purified antigen): Acellular pertussis (aP), Haemophillus influenzae type B(Hib), Pneumococcal (PCV-7, PCV-10, PCV-13), Hepatitis B (hepb)

D. Toxoied (inactivated toxins): Tetanus toxoid (TT), Dipehteria toxoid

E. Viral vactor vaccine: Zaire ebolaviruse

3. Plant Used In Vaccines:

Potatoes

Mason et colleagues conducted the first assay based on a vaccination in potatoes to prevent enteritis caused by Escherichia coli strain LT-B in mice. [16] In the same year, antigens produced by potatoes were tested in rats and human volunteers against pathogens from the non-toxic component (CT-B) and Norwalk virus capsid of Vibrio cholerae enter toxin. [5] The investigation of human immune responses to Norwalk virus capsid expressed in potatoes was used in Tacket's second-phase clinical experiment, which yielded a 95% immunological response. However, a substantial increase was not always achieved. Thanavalas' group hypothesised in 2005 that the potato may be used as an oral reinforcement for the hepatitis B injectable vaccine in people. Furthermore, edible vaccinations have been created as an oral reinforcement to injectable vaccines for animal protection. For example, to protect mink from illnesses, an edible vaccine generated by the mink enteritis virus (MEV) was developed in potatoes.[17,18]

Immunization with potatoes that produce the protein VP60 protected wild rabbits from infection by rabbit hemorrhagic virus (RHDV). [17,19]

Tobacco

To begin, we must emphasize that tobacco isn't necessarily a safe to eat plant; rather, it is utilized as a proof-of-concept model species for the development of safe to eat vaccines. Thus, in 1996, transgenic tobacco (*Nicotiana benthamiana*) plants expressing a protein from the Norwalk virus capsid that causes gastroenteritis were created, [17,20] which resulted in an increase in antibody levels in rats, particularly IgA and IgG. [17,21]

Transgenic tobacco that expressed the viral VP1 protein from chicken infectious anemia was first described in 2007. [17,22] Other tobacco study has verified the ability to target a polypeptide linked to hepatitis B. In this work, researchers were able to trigger a humoral immune response that produced HBsAg; this stimulation resulted in higher blood T-molecular counts, which were then utilized to assess correlations between immunoglobulin A and G humoral responses and vaccine doses. [23] Gómez et. Al [17,24] tried to make the viral antigen in transgenic tobacco more specific. In a study conducted in rats in 2012, transgenic tobacco plants producing HPAIV H5N1 from the avian flu virus offered a boost to IgG stimulation. [17,25,26] Transgenic tobacco plants that express a protein from Eimeriatenella, the agent that causes coccidiosis, as well as transgenic tobacco plants that combat anthrax, have recently been identified. In the latter, the tobacco produced a shielding antigen (PA), which resulted in increased blood IgA and IgG levels in mice. [17,27]

Tomatoes

Within the tomato, a promising vaccine candidate for the coronavirus that causes SARS (severe acute respiratory disease) has advanced (*Solanumly copersicum*).[23] In 2006, researchers discovered that tomatoes expressing the Norwalk floor virus protein that had been dried outside rather than lyophilized before being consumed by rats provided immune protection that was superior to that of potatoes.[17,28] Tomatoes have also been utilized to distinguish CT-B protein from Vibrio cholerae B toxin in leaves, stems, fruits, and other tissues, as evidenced by ELISA and Western blot analysis in leaves, stems, fruits, and other tissues.[28] HBsAg is currently produced in Megha tomatoes, as evidenced by qRT-PCR and ELISA, which is the first record of solid antigen expression in tomatoes. [17,29,30] Human beta-amyloid was first expressed in the tomato in 2008 as a potential Alzheimer's disease vaccine. [17,31] Another study of transgenic tomatoes found that the fusion antigen F1-V was protected from Yersinia pestis, a pathogenic bacterium that causes pneumonic, septicemic, and bubonic plagues. In conclusion, given the wide range of indoor and outdoor production options, tomatoes are now one of the foods with the most potential for use as an edible vaccine.

Lettuce

Experiments on lettuce (*Lactuca sativa*) plants expressing the B subunit of E. coli's thermolabile protein, which is responsible for enteric illnesses in both humans and animals, suggest that this vegetable could be a vaccine candidate. In this investigation, the antigen accounted for around 2% of the total protein identified within the leaves. [17,32] In 2005, lettuce was created that expressed glycoprotein E2 of the typical swine concern hog pest virus. Transgenic lettuce plants that produce anti-hepatitis B virus results are now in the earliest stage of development in Poland. [17,33] Because this meal is a specific type of cuisine, it has the most potential for usage as an edible vaccination.

Rice

Transgenic rice *(Oryza sativa*) flora expressing the B subunit of E. coli result in a large number of antibodies against this subunit, according to a 2007 study. [17,34] Transgenic rice expressing the VP2 antigenic protein from infectious bursa was modified and confirmed to cause an immune response in hens in the same year. PCR and Southern blot research revealed deliberate expression of HBsAg in rice seedlings in 2008. [17,35] Furthermore, in 2008, transgenic rice was produced in parallel to express the E. coli thermolabile toxin B subunit. The bio ballistic technique was used to convert the cells, and the changes in expression were confirmed by PCR. [17,36] Rice production is expected to reach 480 million metric tonnes in 2016/2017. China and India (the world's two most populous countries) will produce and deliver roughly half of that annual manufacturing. [17,37] As rice is an important part of the daily diet, an advanced vaccine for this plant could have a huge impact on the general public's fitness structures.

Carrots

In rats, transgenic carrots (*Daucus carota*) expressing the B subunit of E. coli thermolabile toxin produced IgA and IgG and passed through the intestinal and systemic tiers. [17,38] In 2010, the Helicobacter pylori UreB subunit in transgenic carrots was linked to the usage of vaccination. [17,39] Carrots, in combination with A. thaliana, have also been used in experimental fit for human consumption vaccines for floor HIV antigen expression, with studies in rats revealing higher quality results in treated animals compared to non-treated animals. The use of carrots to treat HIV was once promising, but it is no longer effective because the intake of carrot-derived carotenoids increases lymphocytes, monocytes, and other immunological defences in rats. [17,40] As a result, humans with compromised immune systems may benefit from consuming this anti-HIV vaccination, which is most likely safe for human ingestion. To verify the efficacy of the vaccines, human studies must be conducted.

Soybeans

The B subunit expression of E. coli thermolabile toxin was studied in the soybean (*Glycine max*) endoplasmic reticulum, where a complete antigen level of up to 2.4 percent of the soy seeds resulted in a significant increase in systemic IgA and IgG levels.

Alfalfa

In 1999, a successful oral immunization against virulent foot-and-mouth disease (FMDV) in rats was carried out, providing the first confirmation that long protein chains can be correctly synthesized in the form of uncooked extracts when sufficient plant components are used. [17,41] In a veterinary setting, transgenic alfalfa (*Medicago sativa*) expressing the antigen eBRV4 from hog rotavirus (BVR) VP4 became an edible vaccine. [42] Transgenic alfalfa plants were developed in 2005 to express the hog pest virus glycoprotein E2.

In 2009, transgenic alfalfa was developed that expressed the capsid virus's C protein, which causes hen infections. Different plant species, such as A. thaliana, have evolved the same antigen. [17,43] Echinococcus granulosus Eeg95-EgA31 became expressed in another alfalfa investigation. This protein was isolated and then delivered directly from the leaves to the target organism, [17,44] demonstrating the plant's wide range of veterinary applications.

Corn

In 2012, transgenic corn (*Zea mays*) plants expressing rabies virus antigenic glycoproteins were found to have promising results as a human and animal vaccine. [13,17,45,46] In pigs, promising results have been obtained in the development of vaccinations against the transmissible gastroenteritis coronavirus (TGEV). In studies using transgenic corn as a vaccination, 50 percent of treated pigs developed diarrhea, compared to 75 percent of pigs who no longer responded to the vaccine. The finding that transgenic corn provides partial protection to piglets against medical illness and experimental exposure to the virus. Oral feeding using transgenic maize producing the Newcastle sickness virus fusion protein has been studied in several publications (NDV)

Papaya

To combat cysticercosis caused by Taenia solium, a vaccine based on papaya (*Carica papaya*) fruit was developed in 2007. Synthetic peptides were expressed in 19 transgenic papaya clones. This vaccine was tested on rats, and 90% of those who were given it responded with an immunogenic reaction. Thus, edible Carica papaya vaccines could provide significant relief to both humans and pigs, who are the principal disease vectors, but have yet to be evaluated in these settings.

Quinoa

In 2012, a vaccination suitable for human consumption was developed by producing the VP2 antigen from infectious bursa virus in quinoa (*Chenopodium quinoa*). The vaccination was developed for use in veterinary medicine for roosters. [17,47]

Bananas

The expression of HBsAg in banana plants has been suggested using four different expression cassettes (PHB, PHER, pEFEHBS, and pEFEHER). PCR, Southern hybridization, and reverse transcription PCR were used to investigate expression at various levels. [17,47,48] However, because of the long time it took for the tree to grow, this vaccination was rejected.

Peas

This transgenic plant evolved into a more advanced form of Norwalk virus capsid protein production. Protein buildup of up to 8% of the soluble protein buildup in purple matured fruits, which is found soluble in unripe fruit, will diminish. Expression in plant seeds allowed the antigenic peptide to be stored, resulting in a plant with a high yield of protein expression ranging from 20% to 40%, implying that extraction of prescription medications may no longer require extensive purifying techniques. Pea plants have also been utilized to express the hemagglutinin protein (H), a rinderpest virus-specific PA. The Western Blot stage of expression in leaves ranged from 0.12 percent to 49 percent of the total soluble protein. [17,49] More study is needed to optimize protein expression in transgenic peas.

Apples

In apple leaves, the gene encoding the F protein of the human respiratory syncytial virus (RSV)-F became constitutively expressed. CaMV35S was used to enhance protein expression at a concentration of 20 mg/g of plant tissue. [17,50]

Cherry Tomatillos

For the HBsAg gene of hepatitis B, transgenic cherry tomatillos have been developed. Gene expression was identified throughout the plant; however, it was strongest in the leaves, reaching 300 ng/g fresh weight, and lowest in the fresh fruit, at 10 ng/g fresh weight. In rodents, significant immune activation changes were discovered. [17,51]

Algae

The inexperienced algae *Chlamydomonas reinhardtii* has been utilized as a model to provide large amounts of proteins linked to healing in humans and animals. [17,52] The use of algae for vaccine production appears promising because algae have a very rapid growth rate, their entire systems can be utilized as a raw fabric to create acceptable for eating vaccinations, and there are no restrictions in terms of habitat (sea farms) or fertility parameters. [17,53] Furthermore, there are no concerns about cross-infection with other crops that are connected to the subject. Algae can also be grown in bioreactors [17,54] to further accelerate their already rapid growth. Importantly, the potency of algal vaccines is unaffected by lyophilization, which could ease the global distribution of safe-to-eat vaccinations made from algae. [17,55-57] The version alga C. reinhardtii, in particular, contains FDX1.

Edible Vaccines Developed Through Transgenic Plants:

Table 1: Status of Transgenic Crops Producing Vaccine. [16-23, 33,34,39,40,41]

Product	Plant host	Expression system	Disease	Route of administration	Development stage	Biological source	Family
E.coli LT-B	potato/ maize	transgenic	diarrhoea	oral	phase 1	*Solanum tuberoum /zea maize*	*solanaceae/ poaceae*
Norwalk virus cp	potato	transgenic	diarrhoea	oral	phase 1	*Solanum tuberoum*	*solanaceae*
HBSAg	potato/ lettuce	transgenic	hepatitis B	oral	phase 1	*Solanum tuberoum /lactuca sativa*	*solanaceae/ asteraceae*
Rabies virus	spinach	transient (viral vectors)	rabies	oral	phase 1	*Spinacia oleracea*	*Amaranthaceae*
Newcastle disease virus	tobacco cell suspension	transgenic	Newcastle diseases	Sub cutaneous	USDA approved	*Nicotiana genus*	*solanaceae*
Personalized Anti-idiotype scfus	tobacco plants	transient (viral vectors)	non Hodgkinson lymphoma	Sub cutaneous	phase 1	*Nicotiana benthamian*	*solanaceae*
Personalized Anti-idiotype dcfus	tobacco plants	transient (ON vectors)	non Hodgkinson lymphoma	Sub cutaneous	phase 1	*Nicotiana benthamian*	*solanaceae*
H5N1 influenza HA	tobacco plants	transient (agrobacterium vectors)	H5N1n avian influenza	Intra muscular	phase 1	*Nicotiana benthamian*	*solanaceae*
H5N1 influenza HA/1	tobacco plants	transient (launch vectors)	H5N1n avian influenza	Intra muscular	phase 1	*Nicotiana benthamian*	*solanaceae*
H5N1 influenza HAc1	tobacco plants	transient (launch vectors)	H5N1n swine influenza	Intra muscular	phase 1(ongoing)	*Nicotiana benthamian*	*solanaceae*
Dengue virus type 2 E glycoprotein (EIII)	tobacco plants	agrobacterium tumefaciens	dengue	Sub cutaneous	phase 1	*Nicotiana tabacum cv. MD609*	*solanaceae*
ETEC	corn	-	diarrhoea	oral	phase 1	*Zea mays*	*Poaceae*
FMDA	stylo plant	-	foot and mouth disease	Intra muscular	phase 1	*Stylosanthesguianesis cv. reyan 2*	*Fabaceae*
Taliglucerase alfa	carrot	stable transformation	Gaucher disease	Intra muscular	phase 1	*Daucus carota*	*umbelifers*
Acetyl choline	tobacco	PEGylated	nerve agent attack	Intra muscular	phase 1	*Nicotinanbenthamian*	*solanaceae*
Insulin	safflower	agrobacterium tumefaciens	diabetes	Intra muscular	phase 1	*Carthamus tinctorius linn.*	*compositae*

4. Mechanism:

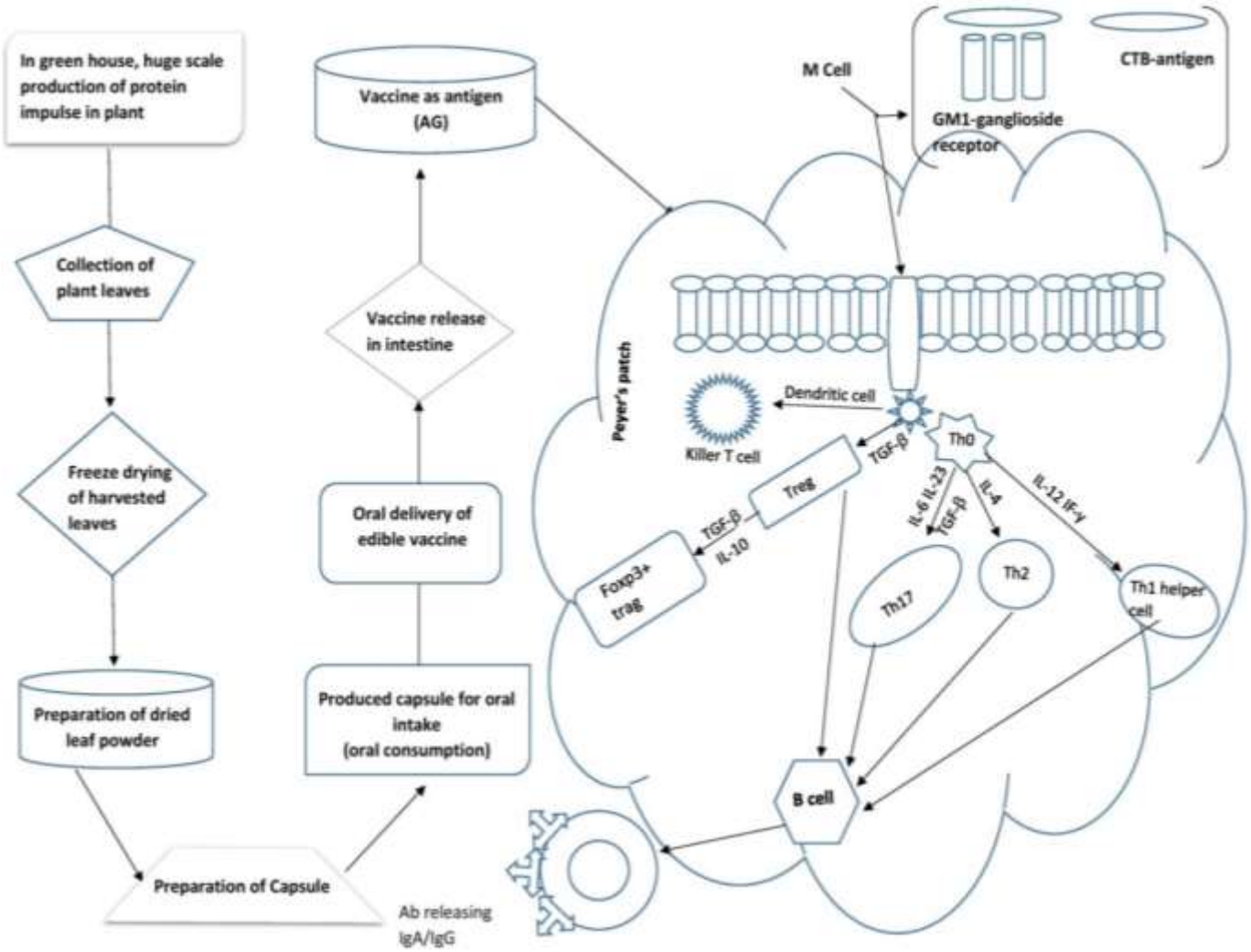

Figure 1: describes outline of edible vaccine development and the mode of action; [58]

Edible vaccine mainly stimulates both mucosal and systematic immunity. Plant tissue releases desired protein in the form of vaccine and absorbed in the intestinal wall. Through capsulation process occur by protective cellular and gastric degradation. Then vaccine absorbed in the form of antigen and the antigen comes in the contact with M cell and M cell passes afterword the antigen to macrophages and B cell. These B cell activates the T cell to provide immune response in the payer's patches and gut associated lymphoid tissue passed on to macrophages and local lymphocyte population generating igG, igE responses. Moreover, it leads to the activation of immune cell and also it moves towards lymph. [58]

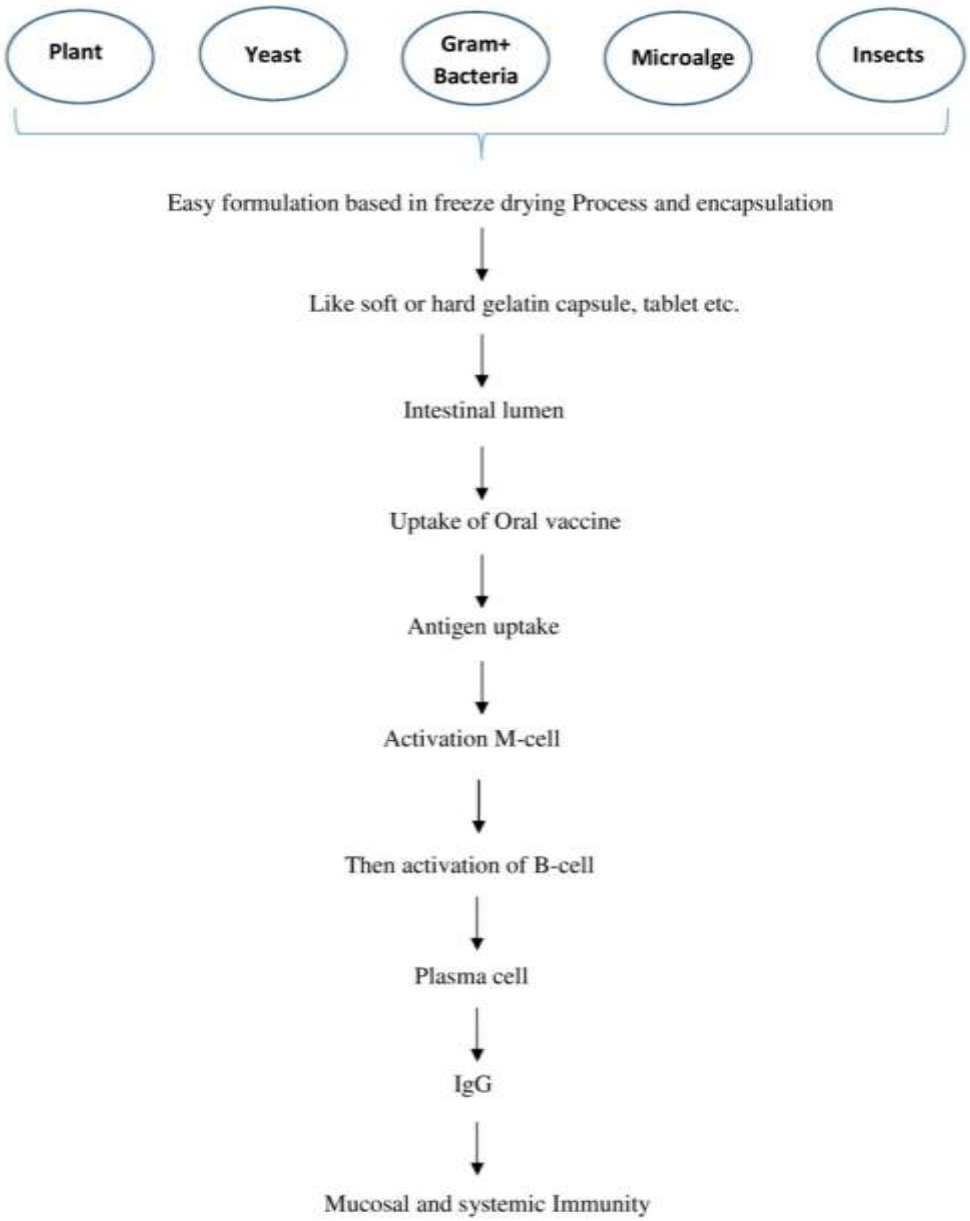

Figure 2: describes overview for Development of Formulation in Edible Vaccine & Its Action; [59-62]

5. Production of Edible Vaccines:

Edible vaccine can be produced by manifestation into the suitable plant cells. Mainly two types of delivery method, first is Direct gene method can be done without combining with vector whereas second method is indirect method it can be combining with vector. Generally, transformation systems are classified as stable or temporary, depending on where the antigen should be united with the cells. [59-64]

***5.1Direct Gene Delivery Method**:*

Direct gene delivery is a straightforward way in the transformation system. The selected DNA and RNA is directly injected into the plant cell in this method. Biolistic approach, also known as gene gun or micro projectile bombardment method, is the most commonly utilized method. This is a vector-agnostic technique. When gene transfer by agrobacterium species medicated transformation is not possible, this is done. [65-67] DNA and RNA serve as a micro carrier in this transformation technique, which is coated with gold or tungsten.

The coated DNA is then loaded into the gene gun and subjected to helium gas at high pressure. Due of the high pressure, the coated DNA moves and penetrates the targeted plant cell. This comes at a high expense and has the potential to destroy the plant. [14 ,68] The biolistic approach can be used to perform chloroplast and nuclear transformations. The two types of antigen expression methods were discussed. [69] Nuclear transformation is the process of incorporating a desired gene into the nucleus of a plant cell through non homogeneous recombination, while chloroplast transformation is the process of injecting the gene into the chloroplast to boost protein expression. chloroplast transformation widely use method for direct gene delivery. [70-73]

Anthrax, Tetanus, Plague, Rotavirus, Cholera, Lyme disease, and Canine Parvovirus are examples of biolistic vaccines.[74]

5.***2 Indirect Gene Delivery**:*

Gene delivery via vector is known as indirect gene delivery. To create the protein of interest, the desired plant cells were infected with plant bacterium or plant virus. Agrobacterium Mediated Gene Transfer is a gram-Ve bacteria that infects plants and transfers its genes to the nucleus of the plant. The two most usually employed species are Agrobacterium tumefaciens and Agrobacterium rhizogenes. The tumor-inducing Ti plasmid is carried by Agrobacterium tumefaciens, while the root-inducing Ri plasmid is carried by Agrobacterium rhizogenes [75]. Auxin and cytokine genes were deleted from Ti plasmids for vaccine manufacturing. This approach has the advantage of yielding a stable integrated antigen. This is a time-consuming method with a low yield. It is, however, simple and inexpensive. Diarrhea, tuberculosis, dengue fever, avian influenza virus, and Ebola are examples of vaccines created using this strategy. [76] Plant that has been genetically modified, this suitable plant virus has been engineered to produce a chimeric gene for viral coat protein. As a result, it's a vector for delivering genetic components to plant cells. This approach causes temporary antigen expression in plants. [12,77] The recombinant virus is a result of viral replication that expresses the desired protein or peptide during viral infection in plants. Vaccine epitopes can also be created and accumulated by altering viral capsid proteins. [78-81] Plant virus-induced infection has several advantages, including rapid recombinant protein expression, facile formation of multiple antigenic copies on the viral particle layer, and the ability to infect wide areas of the plant.[46] However, before the diseased plants are vaccinated, viral replication products must be cleaned from them. Plants die as a result of infection caused by this production procedure. As a result, when the vaccine is generated, another plant must be infected with the virus, and this reinfection technique must be repeated in order to make long-lasting vaccinations. Tobacco Mosaic Virus (TMV), Powder Virus (PVX), Alfalfa Mosaic Virus (AIMV), CMV, and CMV as an expression vector were among the RNA viruses used previously. Engineered viruses, such as the RNA Virus (CMV), make up the majority of the plant virus expression system. Because such viruses do not replicate in mammalian cells, they represent a viable alternative vector for human and veterinary vaccine development. Furthermore, the vaccination antigen obtained is protective against danger infection, as most expression mechanisms indicate. Gemini virus is one of the example of DNA virus are also constructed advance plant expression system as they have single started DNA and also replication double standard DNA in healthy cell. [82]

6. Advantages and disadvantages:

6.1 Advantages

1) In comparison to traditional vaccines, edible vaccines do not require a complex framework for purification, sterilization, packaging, or distribution, resulting in lower long-term expenses.

2) Vaccine distribution and management are less difficult than with conventional vaccines.

3) Conception of a raw material is another advantage of plant-based vaccine.

4) In terms of animal immunization, edible vaccines appear to be more promising

5) Don't need to Cook.

6) Not much storage conditions are required as compared to normal vaccine.

7) Children's compliance is improved.

8) Low-cost vaccine manufacture is a possibility.

9) Reduction in the necessity for surgery and sterile injection situations.

10) easy to accessible.

11) Ease of administration.

12) Process of sterilization is not necessary for edible vaccine.

13) It is high demand as administration through oral route.

14) Efficient mode of action for immunization.

15) For producing edible vaccine, machines and equipments are not required If easily grow in cell culture compare to economical method.

6.2 Disadvantages

1) Development of immune tolerance particular in protein and peptides.

2) Dosage form consistency varies from plant to plant, generation to generation, and fruit to fruit.

3) Stability of vaccine in fruit is unknown.

4) Dose ratio will be differed because of several factors like plant, protein content and ripeness of fruits.

5) Difficult in selection of suitable plant.

6) Main element which we required it should not be Cook.

7) Palatability is also a major issue.

8) Not suited for children under the age of one.

9) There is a need to make a distinction between vaccine fruits and regular fruits.

10) People may develop an allergy to the fruit or vegetable expressing the foreign antigen.

11) Consistency of same quality vaccine production might not be guaranteed. [83-99]

7. Future prospective:

Required to more related study to increase stability of all type of edible vaccine. Edible vaccine includes limited plant for the production of vaccine. In recent and further study requires to increase the species and varieties of plants with fruits which having more acceptance in uncooked condition.[100] By development of edible vaccine, food can be converted into functional food or nutraceutical food. By further study, edible vaccine should be converted into cost effective medicine easily available to all.[101] Edible vaccine technology should be incorporated in prevention of life threatening diseases like HIV, TB, Corona, Malaria, Cancer, Heart disease, Diabetics, Dengue and Respiratory diseases.[102] One of the novel scope for edible vaccine is multiple gene expression in single edible vaccine which may be useful to prevent verities of disease in single dose/ vaccination it means intake of one vaccinated immuniated fruit or vegetable gives the protection from many disease like , HIV, TB, corona, malaria, Cancer, heart disease, diabetics,

dengue and respiratory diseases. The future of edible vaccine also depends on various who guidelines and its fulfilment. [103]

8. Conclusion:

Fruit type of edible vaccine is suitable for nutritional supplement along with the main immunization action. It is one of the best options from convenience injection. It is a one of the part of fruits so easier to intake. Fruit derived vaccine has many benefits as compared to traditional vaccine. Fruit derived edible vaccine have more secure and greater effective vaccination.

Conflict of Interest:

The authors have no conflict of interest.

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