Available online on 30.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Edible Vaccines: Trigger of Body's First Line Defense

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ABSTRACT

Vaccines are used as protective agents from various diseases. The major reason to prepare vaccines are to digest the macromolecule of proteins in stomach considering of high pH . To overcome this issue a scientist named Arntzen developed the theory of edible vaccines. EVs are developed by genetic technology; in this the genes are introduced directly to the plants in various methods. The developed plant contains coded protein which acts as a vaccine. Purchasing at low cost leads to the prevention of various diseases like malaria, measles, hepatitis B , cholera, HIV and anthrax

Keywords: Edible vaccines, Antigens, Oral immunization, Immunity.

Article Info: Received 08 July 2019; Review Completed 12 Aug 2019; Accepted 22 Aug 2019; Available online 30 Aug 2019

Cite this article as:

Santosh Kumar R, Chandra Kiran C, Edible Vaccines: Trigger of Body's First Line Defense, Journal of Drug Delivery and Therapeutics. 2019; 9(4-A):811-814 **http://dx.doi.org/10.22270/jddt.v9i4-A.3619**

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INTRODUCTION

Vaccines [1-5]

Vaccines have been revolutionary for the prevention of infectious diseases Vaccines. Plant-based vaccine which is the immune-biological substance give resistance against infectious and non-infectious diseases. The administration of a vaccine to help the immune system to develop protection from a disease is referred as vaccination and it is a form of immunization. Vaccination is given to some patients as they show reoccurring of the disease, there by reducing the cost of expensive treatment procedures. Edward Jenner is the father of Immunization and he was the first to study inoculation of cowpox virus prevents small pox in human. There are Various routes of administration of vaccines, including oral, nasal, and parenteral routes such as intramuscular (IM),subcutaneous(SC), and intradermal (ID). Most of the commercial vaccines are administered by IM or SC routes. A number of new different vaccines - such as live/attenuated bacterial or viral vaccines, killed bacterial suspension, toxins produced by bacterial toxoids and rickettsial suspension - have been developed.

Difficulties in traditional vaccine systems [6-7]

The major limitations of the standard vaccines are their storage, transport under strictly controlled conditions.

Criteria for standard oral vaccine system:

i. Desired antigens should be present in sufficient quantities

ii. Stability of expressed antigen at room temperature for a long time

iii. Protective immunity must be induced by the vaccine

iv. Should withstand degradation by enzymes in the stomach.

The Evolution of plant-derived vaccine technology [8-10]

The standard vaccines have many limitations and the newer vaccines are developing to have flexibility in administration, storage, transportation and ultimately cost-effective. There are plants and plant viruses which are genetically developed vaccines against diseases. Transgenic research developments have created production of transgenic plants expressing antigenic proteins as they are induced by plant transgenic vectors. This will help to produce special vaccines with high anti-disease ability.

The positive effects of edible vaccines can decrease the potential hazards such as toxic compounds, responses to allergy, and risk of attenuated strains reverting to pathogenic strains. The Edible vaccines have various functions for either individual animals or humans by providing long lasting immunity without risk of relapse reaction and faulty techniques; there is lack of information about their production and mechanism of action.

Concept of EVs[10-14]

The concept of edible vaccines was developed by Arntzen in the 1990s. *Streptococcus mutans* bacteria causes dental caries and stimulation of a mucosal immune response will stop the bacteria from colonizing the teeth and protects against tooth decay. Vaccine antigens using the methods of molecular biology can administrate the edible transgenic parts orally. The development of genes can be introduced into plants and expressed in the plant tissues including the edible components. This is known as "transformation" and the genetically modified plants are known as "transgenic plants." The vaccine can be delivered by intake of the edible part of the genetically modified plant, or the high-yield production of refined protein for oral delivery edible vaccines are like unit preparations as they contain antigens, however, bear no genes that might change whole pathogens to cause serious harmful effects to humans . Thus, they don't create any infection, assuring its safety, particularly in immune-compromised patients. The production is very economical, less expensive, heat stable, do not require cold temperature maintenance, can be stored near the site of use and can easily be scaled up. They don't require syringes and needles, using standard methods these can be grown regionally and don't require capital-intensive pharmaceutical manufacturing facilities.

Properties of an ideal vaccine [15-16]

i. It should not be toxic.

ii. It should have very low levels of side effects in normal individuals.

iii. It should not cause problems in individuals with impaired immune system.

iv. It should produce long-lasting humoral and cellular immunities.

v. The vaccination technique should be simple.

vi. The vaccine should be less expensive.

vii. No contamination in the environment.

viii. It should be effective and affordable.

Advantages and disadvantages of EVs [17-18]

Advantages

i. They can be produced economical.

ii. They can be easily administered by eating the part of the plant.

iii. They can be stored at normal room temperature.

iv. If the local crop of a particular area produces vaccine then it can eliminate the distribution and transportation.

v. They trigger the body's first line of defense.

Disadvantages

i. The plants which are selected with stable antigen production can be a time consuming task and expensive.

ii. Lack of knowledge about plant biotechnology leads to negative public opinions.

iii. Development of oral tolerance to vaccines and difficulty in administration of standard dose are additional limitations.

Mechanism of action [19-20]

The aim of oral vaccination is to stimulate mucosal and systemic immunity against foreign particles. The orally induced edible vaccine undergoes the mastication process and the high amount of plant cell degradation process in the intestine and results in action of digestive or bacterial enzyme on every vaccine. The essential source of Ig A producing plasma cells are peyer's patches(pp).They have the ability to populate mucosal tissue and provides as mucosal immune effector site. The collapse of edible vaccine near peyer's patches consisting of 30-40 lymphoid nodules on the outer surface intestine and consists of follicles. This follicles acts as a area from which antigen penetrates the intestinal epithelium thereby accumulating antigen within organized lymphoid structure. The antigen then linked with M-cell. M cell crosses the antigen to macrophages and B cell. The T cell is activated by B cell to provide immune response. Immunity is activated by the edible vaccine.

Candidates for EVs [20-25]

Edible parts of various species of plants like grains or fruits are utilized for the desired interest of antigen. For high levels of antigenic protein expression the cereals like rice and maize, fruits like banana, leaves of many plants and tubers like potatoes, tomatoes, soybean seeds, cowpea, pea, carrot, peanut, and lettuce are used extensively. The factors considered while selecting a vehicle for the vaccine are: Plant must be hardy, it should be palatable, relished and it should be indigenous, easily available and transformation is done easily. The main goal of using transgenic plants as production systems for animal and human vaccine antigens is to make it easier and delivery of immunizing antigen so the mass immunization can be gained against infectious disease.

Banana [26]

Bananas are good choice for EV as they are sterile and do not pass the genes from one banana to another. Bananas grow in tropical climate. Most third world countries are found in this climate. It does not need cooking. Even if it is cooked the proteins are not destroyed and can be eaten raw . It is affordable, have high vitamin A content which boosts immune response and can be grown in developing countries. It takes 2-3years for a tree to mature and transformed tree takes 12 months for fruit bearing and spoils quickly after ripening.

Rice [4]

EV using genetically varied rice is used in treatment of cholera. Cholera vaccine is present which gives short-lived protection and it needs refrigeration. A strain of rice can serve as a vaccine and lasts more than year and half at room temperature. Due to low level of allergic potential it is used as pediatric food but grows slowly and needs specialized glasshouse condition.

Maize [14]

Maize plants produce a protein that is used to develop the hepatitis B virus vaccine. It is affordable and need not be refrigerated. A major disadvantage of this vaccine is it causes degradation of proteins.

Potato [27]

Potato based vaccine used to fight the Norwalk virus (stomach virus), which is spread by contaminated water and food and causes severe abdominal pain and diarrhea. Potato has been also served as a vehicle for diabetes-related proteins, the vaccine against a strain of *Escherichia coli,* cholera vaccine. A potato based vaccine has advantages such as safely stimulating antibodies, affordable, and stored for a prolonged period without refrigeration. The major limitation

is it needs cooking which can denature antigen and decrease immunogenicity.

Tomato [28-30]

Tomato as a vector develops the vaccines against anthrax, rabies and HIV/AIDS. It has advantages such as growing quickly, cultivated broadly, heat-stable, and high vitamin. A composition may boost immune response. Antigen which contains powders can be filled into capsules and with no requirement of storage and transportation facilities. However, it has a disadvantage as it spoils quickly.

Tobacco[31-32]

Human papilloma viruses (HPV) is the agent for causing cervical cancer and also skin, head, and neck tumors. HPV distinct classes more than 150 are known. HPV 16 and 18 are the most common HPVs found in cervical carcinomas. The E6 and E7 virus proteins are known as oncoproteins. Tobacco plants are a good in evaluating recombinant proteins and can be harvested many number times in a year. Due to high level toxic alkaloids composition, it causes more toxicity.

Miscellaneous candidates [33-40]

Some plants which can be served for vaccine delivery are lettuce , soybean and wheat.

APPLICATIONS OF EVs

Malaria [40-42]

Many strategies have been tested to fight malaria and many attempts have been made to introduce a malaria vaccine . Three antigens are in development of EVs, merozoite surface protein (MSP) 4 and MSP 5 from *Plasmodium falciparum* and MSP4/5 from *Plasmodium yoelii*. It is suggested that antigen response level in plants is low; this requires administration of a large quantity of plant material to achieve the desired immunity. However, due to the high degree of antigen expected to be necessary, it is likely that strong adjuvant should be required.

Measles[43]

The vaccine which is used currently produces 95% seroconversion in individuals who are over the age of 18 months during the time of vaccination. Hence, refrigeration is necessary for its storage. Measles virus hemagglutinin (MV-H) from the antigen edmonston strain was selected for the development of an EV, which can be transformed into tobacco plant by plasmid/vector. Tobacco expression when it is feed to mice MV-H could attain antibody titers 5 times the level is protective for humans and they also show secretory IgA in their feces. It is studied that transgenic carrot plant is used to produce viral antigens for the development of measles vaccine.

Cholera[44-45]

Genetically modified potatoes showing CTB produces both serum and secretory antibodies when fed to mice. Since people eat only cooked potatoes, the effect of boiling on the properties of CTB expressed in transgenic potatoes was examined. It was evidenced that, over half of the vaccine protein survived in its biologically active form even after boiling for five minutes and this proves that cooking does not always inactivate EVs.

Norwalk virus [46]

Nineteen out of 20 people when administered transgenic potato expressing Norwalk virus antigen developed seroconversion. Genetically engineered bananas and powdered tomatoes expressing Norwalk virus are under development phase to fight Norwalk virus.

HIV[47-49]

Genetically modified tomatoes were developed by injecting two HIV protein genes along with promoters such as CaMV with a needle and the expressed protein was confirmed by polymerase chain reaction in various parts of the plant, including the ripe fruit, as well as in the second- generation plant.

Future directions

The future of edible vaccines depends on these factors:

• Socio-cultural acceptability of genetically changed plants,

• Stability of genetically modified varieties and

• Proper segregation of transgenic plants, prevention of environment contamination and prevention of potent side effects of transgenes as allergens.

EVs can be safe and effective modes of immunization and are better as compared to the traditional vaccines when mass production, distribution, and delivery are concerned. Therefore, there is a need for the development of a cost-effective, efficient and safe delivery.

CONCLUSION

EVs are the milestone in the branch of biotechnology for developing inexpensive vaccines that are particularly useful in immunizing people in developing countries, where high cost, transportation and the need for cold storage conditions, are hampering effective vaccination programs. Edible plant-based vaccine may lead to a future of safer and more effective immunization. The expectation is that EVs may be fully grown in many of the developing countries where they would actually be used.

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