



## A review on natural way of vaccination: plant derived edible vaccines

Arif Khan<sup>1\*</sup>, Asad Khan<sup>1</sup>, Irfan Khan<sup>1</sup>, Muhammad Aamir Shehzad<sup>1</sup>, Waqar Ali<sup>1</sup>, Atif Muhammad<sup>2</sup>, Muhammad Akif<sup>3</sup>

<sup>1</sup>*Department of Biotechnology, Abdul Wali Khan University Mardan, Pakistan*

<sup>2</sup>*Department of Environmental Science, Abdul Wali Khan University Mardan, Pakistan*

<sup>3</sup>*Department of Chemistry, Abdul Wali Khan University Mardan, Pakistan*

**Key words:** Edible, vaccines, plants, Immunity, transgenic.

<http://dx.doi.org/10.12692/ijb/15.4.95-100>

Article published on October 08, 2019

### Abstract

Immunizing human or animals with edible plants is an evolving tool that seems to grip countless potential. The selected/desired antigen of pathogens (HIV, tuberculosis etc) are inserted to the selected host plant by transformation technique to form a transgenic plant. Edible vaccines grip countless promise as a profitable, easily managing, can be store easily, unlikely or unable to fail and sociocultural gladly sustainable, particularly for the poor emerging nations. An edible vaccine takes the place of sore immunization methods. Compare to conventional vaccine, edible vaccine is inexpensive, needle free, eradicates the requirement for preservation, harmless, may be stored nearby to place of usage, and deliver mucosal and complete immunity. For the enhancing immunity in human and animal against Various type of infectious diseases such as cholera, measles, FMD and hepatitis B there are numerous types of edible vaccines are being developed. Edible vaccines also help to overpower auto immunity diseases alike type-I diabetes. Immunization generations and giving malnutrition have the dual advantages of edible vaccine. If the notable problem and challenges may be triumph over It also can bring about a destiny of more secure and further effective immunization.

\* **Corresponding Author:** Arif Khan ✉ [Arifkhan5897@gmail.com](mailto:Arifkhan5897@gmail.com)

## Introduction

Vaccine has been emerged as effective tool against various infectious diseases as it delivers effective and direct defense opposed to unnecessary diseases and deaths. Due to constraints like high cost and storage, vaccination cannot protect lives of millions of peoples in poor and developing countries all over the world. Still about 20% of newborn remain unimmunized which lead to roughly 2 million needless expiries(deaths) annually, particularly in the far reaching and poor portions of the globe(Fischer and Emans, 2000). The main problem to be solved is the boundaries on the production of vaccine, supply and distribution (Ramsay *et al.*, 1999). For certain infectious disease immunization does not exist either the are very expensive or unreliable such as immunization via DNA vaccines is substitute but the method is expensive and some undesirable immune responses arise. Apart from being expensive the other problem is the vaccine storage and transportation, as many of them need refrigerator. Therefore, to eliminate these problems there is search for widely acceptable, storable, easily administrable, reliable and especially their delivery systems in developing countries. The world health organization in 1990's presented a task of emerging cheap method of oral vaccine production that do not need of refrigeration requirement. To the people of underdeveloped nations, the oral vaccines is more inexpensive and accessible. Researcher created the concept of edible vaccines in which eatable parts of the plant using as a factory for the vaccines manufacturing (Phoolcharoen *et al.*, 2011). The advantages of edible vaccines are the lack of contamination that can happen during traditional mammalian culture cells, one of the helpful characteristics of these vaccines is that they do not involve any syringes or needles, it is easy to deliver to the body and socially acceptable to the public. The specific antigen is protected by the cell wall of plant cells and cannot be damaged by gastric enzymes and can easily reach the bloodstream and activate the mucosal and systemic immunity. Hence, as an alternative have to produce for traditional vaccines, it was imagined that for efficient production system

plants could be promising agents for vaccines. Which in turn gave rise to the novel concept of edible vaccines.

### *Edible vaccines, its uses and prospective*

#### *Early progresses of the edible vaccine development*

The idea of edible vaccines was established in the 1990s (Tanghe *et al.*, 2006). The edible vaccine first demo has taken in the tobacco on the mutants of bacterium streptococcus, in the mutants the surface antigens was expressed. Dental caries is caused by this bacterium, it was predicted that the stimulation of a mucosal immune response could prevent the bacteria from colonizing the tooth and therefore defend in opposition to tooth decay.

#### *Edible vaccines*

Edible vaccines are animal-based and transgenic plants manufacture that contain agents which generate animal's immune response. Simply, edible vaccines are animal or plant made pharmaceuticals. Edible vaccines are the preparations of subunit where they are prepared to contain antigens which might be produced in genetically altered plant and supplied to the plants parts which is able to eat (Artnzen, 1997). Transgenic plants in the edible vaccines are used as vaccine production system. In plants the genes can be expressed which encoded the antigens of viral and bacterial pathogens wherein they maintain the native immunogenic properties. Antigenic proteins are the composition of Edible vaccines and pathogenic genes are deficient, it works in the comparable manner as the inserted DNA vaccine. Therefore, after the ingestion of edible vaccine it become assimilated and then protein move in the blood stream, the infectious protein is neutralizing due to the immune response and makes a reminiscence spot of it.

Development of vaccines (edible vaccines) through the transformation process in which selected desired genes incorporated into plants and then allowing these altered plants to produce the encoded proteins. The plants which is altered through the process of transformation is called transgenic plants. The introduction of selected genes into selected plants

through different plants genetics methods such as Electroporation method, Micro projectile bombardment method, *Agrobacterium tumefaciens* Plasmid vector carrier system. Edible vaccine can additionally motive a destiny of harmless and additional efficient immunization (Tripurani *et al.*, 2003).

#### *The efficiency affecting factors of edible vaccines*

Choosing of appropriate, easily cultivated and profitable plant species and stable and harmless antigen. It has Toxic, Allergic problems and Observations of public. Vaccine monitoring authority and instructions and Conveyance and medicating problems.

#### *Edible vaccines derived from fruit*

The main and important part of a flowering plant is fruit that originates from flower particular tissues, mostly a single ovary. For edible vaccine fruit fruits is the most appropriate because fruits have no requirement to chef them. The heat during cooking denatures the protein present in edible vaccine. For edible vaccine production mostly papaya and banana are used (Daniell, 2007).

The earliest fruit which uses for the plant transgenic programs banana is one of them banana. Papaya is an extensive tropical and semi-tropical fresh edible fruit. Papaya and banana are producing rapidly, cheap, commonly produces in emerging nations, high quantity of vitamin "A" is present and because of the sterile condition in banana the genes not transfer from one banana to another.

A study stated that the expression of foreign proteins (vaccine) At the time of ripening in the banana fruit MaExp1 promoter could be an important tool (Hassler, 1995). There are some drawbacks of banana using as an edible vaccine that it quickly spoils after ripening and the amount of protein contain very smaller. The perfect edible vaccine would be inexpensive, having long-term cellular and humoral resistances, nonpathogenic and nontoxic, the level of side effects is very low, contamination level of the

environment is level, in the individuals don't cause the problems with impaired immune.

#### *Edible vaccines for diarrhea*

##### *Transgenic potato as edible vaccines*

For the first time in 1997, the trail of human edible vaccines was conducted. The causative agent of diarrhea, E. coli B-subunit warmth labile toxin was expressed within potato. Among of the total 11 individuals, 10 were examined to have four-fold increase in serum antibodies against that toxin (Tacket *et al.*, 1998, Tacket *et al.*, 2004). After two years, scientist test at Cornell University showed a similar clinical trial of an edible vaccine. They expressed antigens of Norwalk virus (that causes diarrhea) in potato and similar efficacy was reported(Tacket *et al.*, 2000).The only limitation of this type of edible vaccine is the possible denaturation of protein during cooking process. However, partial boiling of potato can reduce the denaturation of the protein.

##### *Transgenic tomatoes against diarrhea*

Researcher introduced transgenic tomatoes at the Cornell University against the Norwalk virus which cause severe diarrhea. Surface protein which produced tomatoes specific to the disease causative virus. Scientist have reported immune response to the virus in mice when transgenic tomatoes fed to the mice (Chaitanya and Kumar, 2006).Similarly, banana was studied for the expression of transgenic protein as it eliminates the cooking process as well as it is locally growing plant. This expression required the identification of particular promoter. Moreover, expression of rabies glycoprotein in spinach and hepatitis B surface antigen in lettuce and potato has been reported (Yusibov *et al.*, 2002)(Kapusta *et al.*, 1999, Richter *et al.*, 2000).

#### *Benefits of fruit derived edible vaccine*

The edible vaccines are cost-effective in bulk scale production/transportation. Eliminate requirements like cooking. Heat-stable, eliminate the condition of refrigeration. Enhanced compliance in children. Reduced requirement of medical personnel and

sterile injection conditions. Storage at use-site and Sophisticated administration

#### *Constraints of Edible Vaccine*

*The fruit to fruit or plant-to-plant vaccine dosage is not compatible. The stability of the vaccine within the fruit is not known and improved immune sensitivity to peptide or protein vaccine. The dosage of vaccine is variable and difficulty in plant selection. Another issue is sweetness and not suitable for infants. Ethical and ecological issues regarding GM plants is also a constraint of edible vaccines.*

#### *Applications*

Several clinical trials were conducted to authenticate the potential that the vaccines are suitable for human consumption. Numerous human and animals' infectious disease such as hepatitis B, measles and cholera have been examined for edible vaccines. Furthermore, vaccines against autoimmune diseases such type-I diabetes were also studied (Prakash, 1996). Prodigene a biotech company (US) has a patent for edible vaccine against Hepatitis B disorder while college of Yale has a patent for Vaccine in opposition to invertebrates like insects and arachnids (Waghulkar, 2010). Foot-and-mouth disease (FMD) is among the leading contagious viral illnesses of wild reflective and domestic animals. FMDV is a positive sense single stranded RNA virus that contain four capsid proteins VP1, VP2, VP3 and VP4. The VP1 protein is potential target to be used as edible vaccines via stimulating immune system to produce VP1-neutralizing antibodies necessary for immunization. The capability of such type vaccines such as a subunit PMV candidate, in tobacco, potato and tomato (Santos *et al.*, 2002). Potato-based totally vaccine towards hepatitis B have reported that the amount of HBsAg wished for one dose will be accomplished in a unmarried potato. tiers of unique antibodies appreciably exceeded the protective level of 10 mIU/mL in humans (Domansky *et al.*, 1995).

#### *Future prospective*

It is problematic in this region of science to expect how rapidly new products turns into to be had and be

well-known by way of the purchaser. In principle, now it's possible to transfer a gene of an organism into any plant, to express that new product in any part of the plant, be it seed, root, tuber or leaf. Progressively, food is being measured not just a basic nutrition source but slightly as a product with unique medicinal properties (Kay *et al.*, 1997).

So, known as "functional food". as an instance, changes inside the basic composition of the kind deliberated above may be accompanied by means of more radical changes; influential human growth factors have been produced in fruit (Matoh *et al.*, 1996), and leaves (Lee *et al.*, 1997) and might be fairly easy to reduce the level of poisonous compounds for example oxalate (Nakamura *et al.*, 1996), a compound that have to be averted by way of those stricken by urolithiasis – the deposition of kidney and bladder stones. As we pass towards food with greater precise health benefits (Knauf and Facciotti, 1995), and the opportunities created via such products, the issue of prediction lies no longer a lot in scientific world but as an alternative in estimating business fulfillment.

#### **Conclusion**

For edible vaccination fruit act as a transporter having dual advantage, the one advantage is the producing immunization and the other advantage is giving the malnutrition. It's a substitute of painful immunization procedures. Fruit derived vaccine (edible vaccine) has many benefits as compared to traditional vaccine. Edible vaccine is inexpensive, needle free, attractive to children, may be stored nearby the place of usage, harmless, deliver the systematic and mucosal immunity. Fruit derived edible vaccine may additionally motive a destiny of more secure and greater effective vaccination if massive and important challenges may be overcome.

#### **References**

- Artzen C.** 1997. Edible vaccines. Public health reports **112**, 190.
- Chaitanya VK, Kumar JU.** 2006. Edible vaccines. Sri Ramachandra Journal of Medicinal **1**, 33-34.

- Daniell H.** 2007. Chloroplast transgenic approach to express and purify human serum albumin, a protein highly susceptible to proteolytic degradation. Google Patents.
- Domansky N, Ehsani P, Salmanian AH, Medvedeva T.** 1995. Organ-specific expression of hepatitis B surface antigen in potato. *Biotechnology letters* **17**, 863-866.
- Fischer R, Emans N.** 2000. Molecular farming of pharmaceutical proteins. *Transgenic research* **9**, 279-299.
- Hassler S.** 1995. Bananas and biotech consumers. *Bio/Technology* **13**, 417.
- Kapusta J, Modelska A, Figlerowicz M, Pniewski T, Letellier M, Lisowa O, Yusibov V, Koprowski H, Plucienniczak A, Legocki A.** 1999. A plant-derived edible vaccine against hepatitis B virus. *The FASEB journal* **13**, 1796-1799.
- Kay RF, Madden RH, Van Schaik C, Higdon D.** 1997. Primate species richness is determined by plant productivity: implications for conservation. *Proceedings of the National Academy of Sciences* **94**, 13023-13027.
- Knauf VC, Facciotti D.** 1995. Genetic engineering of foods to reduce the risk of heart disease and cancer. *Nutrition and Biotechnology in Heart Disease and Cancer*. Springer.
- Lee HL, Padmanabhan V, Whang S.** 1997. Information distortion in a supply chain: the bullwhip effect. *Management science* **43**, 546-558.
- Matoh T, Kawaguchi S, Kobayashi M.** 1996. Ubiquity of a borate-rhamnogalacturonan II complex in the cell walls of higher plants. *Plant and cell physiology* **37**, 636-640.
- Nakamura Y, Ito K, Isaksson LA.** 1996. Emerging understanding of translation termination. *Cell* **87**, 147-150.
- Phoolcharoen W, Bhoo SH, Lai H, MA J, Arntzen CJ, Chen Q, Mason HS.** 2011. Expression of an immunogenic Ebola immune complex in *Nicotiana benthamiana*. *Plant biotechnology journal* **9**, 807-816.
- Prakash C.** 1996. Edible vaccines and antibody producing plants. *Biotechnology and Development Monitor* **27**, 10-13.
- Ramsay AJ, Kent SJ, Strugnell RA, Suhrbier A, Thomson SA, Ramshaw IA, kent SJ, Strugnell RA, Suhrbier A, Thomson SA.** 1999. Genetic vaccination strategies for enhanced cellular, humoral and mucosal immunity. *Immunological reviews* **171**, 27-44.
- Richter LJ, Thanavala Y, Arntzen CJ, Mason HS.** 2000. Production of hepatitis B surface antigen in transgenic plants for oral immunization. *Nature biotechnology* **18**, 1167.
- Santos Majd, Wigdorovitz A, Trono K, Ri'OS, RD, Franzone PM, GIL F, Moreno J, Carrillo C, Escribano JM, Borca MV.** 2002. A novel methodology to develop a foot and mouth disease virus (FMDV) peptide-based vaccine in transgenic plants. *Vaccine* **20**, 1141-1147.
- Tacket CO, Mason HS, Losonsky G, Clements JD, Levine MM, Arntzen CJ.** 1998. Immunogenicity in humans of a recombinant bacterial antigen delivered in a transgenic potato. *Nature medicine* **4**, 607.
- Tacket CO, Mason S, Losonsky G, Estes MK, Levine MM, Arntzen CJ.** 2000. Human immune responses to a novel Norwalk virus vaccine delivered in transgenic potatoes. *The journal of infectious diseases* **182**, 302-305.
- Tacket CO, Pasetti MF, Edelman R, Howard JA, Streatfield S.** 2004. Immunogenicity of

recombinant LT-B delivered orally to humans in transgenic corn. *Vaccine* **22**, 4385-4389.

**Tanghe A, Van Dijck P, Thevelein JM.** 2006. Why do microorganisms have aquaporins? Trends in microbiology **14**, 78-85.

**Tripurani SK, Reddy N, Rao KS.** 2003. Green revolution vaccines, edible vaccines. African Journal of Biotechnology **2**, 679-683.

**Waghulkar V.** 2010. Fruit derived edible vaccines: Natural way for the vaccination. International Journal of Pharmaceutical Technical Research **2**, 2124-2127.

**Yusibov V, Hooper D, Spitsin S, Fleysh N, Kean R, Mikheeva T, Deka D, Karasev A, Cox S, Randall J.** 2002. Expression in plants and immunogenicity of plant virus-based experimental rabies vaccine. *Vaccine* **20**, 3155-3164.