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Fruit the carrier for vaccination: A review

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Abstract
A vaccine is a biological preparation that improves immunity against a particular disease. Vaccine contains weak or a killed pathogens of bacteria or virus which stimulates our immune system. Edible vaccines are genetically modified crop, in which edible part generally fruit or vegetables act as a vector of vaccine. It is plant based orally delivered vaccine. In edible vaccine production selected gene for antigenic proteins introduced into plant through various plant genetics techniques. Induced gene alters the plant to manufacture the encoded protein. Edible vaccine contains the antigen protein and devoid of pathogenic genes hence edible vaccine assures its safety. Fruits are most suitable for edible vaccine as there is no need to cook them. Cooking i.e. heat denatures the protein of edible vaccine. Banana, Papaya is most suitable for edible vaccination as it grow quickly, content high amount of Vitamin A which boost immune response. However, it spoils rapidly after ripening and contains very little protein. An edible vaccine replaces painful vaccination procedures. Compare to conventional vaccine, edible vaccine is needle free, low cost, eliminates the need for refrigeration, can be stored near to site of use, safe, and provide mucosal and systemic immunity. Edible vaccine are being developed for number of human and animal infectious disease like hepatitis B, cholera, measles, FMD etc. They may also help to suppress auto immunity diseases like type-I diabetes. Fruit derived edible vaccines have double benefit of creating immunization as well as treating malnutrition. It may lead to a future of safer and more effective immunization if significant challenges can be overcome.

Keywords: fruit, vaccination, banana, papaya, immunization

Introduction
Immunization is most effective health interventions as it provides direct and effective protection against preventable morbidity and mortality. A vaccine is a form of immunization in biological preparation that improves immunity to a particular disease. The process of distributing and administrating vaccines is referred to as vaccination. Edward Jenner in 1796 evaluated inoculation of cowpox virus in humans to prevent small pox in humans successfully. A vaccine typically contains an agent that resembles a disease causing microorganism, and is often made from weakened or killed forms of the microbe. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters (Hafiz *et al.* 2015) [19].
Vaccines have accomplished near miracles in the fight against infectious disease but many of the vaccination techniques cannot reach to save the lives of millions peoples in developing and poor nations around the world as the cost of vaccine production, storage is out of reach for them. In this context in 1990's world health organization gave a challenge of developing inexpensive production of oral vaccination technique that don't need refrigeration. Oral vaccines are more affordable and accessible to the inhabitants of developing countries. Charles J. Arntzen (Biodesign institute, Arizona State University) invented the idea of using edible plant parts as a factories for synthesizing vaccines known as ''edible vaccines'' system.

Edible Vaccine
Edible vaccines are like subunit preparations in that they are engineered to contain antigens that can be grown in genetically modified plants and delivered through the edible parts of the plant (Arntzen 1997) [2]. In the edible vaccine, *Transgenic plants* are used as vaccine production systems. The genes encoding *antigens of bacterial and viral pathogens* can be expressed in plants in a form in which they retain native immunogenic properties. Edible vaccines are composed of antigenic proteins and are devoid of pathogenic genes It work in the same way as the injected DNA vaccine. Thus, they have no way of establishing infection, assuring its safety. When edible vaccine was consumed it get digested and the proteins enters the blood stream, the immune response neutralizes the pathogenic protein and makes a memory mark of it.

Edible vaccines are prepared by introducing the desired gene into plants (Transformation) and inducing these genetically modified plants (Transgenic plants) to manufacture the encoded protein. There is need to select the plant species according to disease and to develop the varieties having odd color or size of edible parts so that it can be easily identified as edible vaccine. Desired gene encode putatively protective vaccine antigens from viral, bacterial, and parasitic pathogens that cause disease in humans and animals. Gene introduce into selected plants by various plant genetics techniques like *Agrobacterium tumefaciens* Plasmid vector carrier system, Micro projectile bombardment method, Electroporation method. Edible plant-derived vaccine may lead to a future of safer and more effective immunization (Sambasiva Rao *et. al*. 2011) [43].

Factor affecting efficiency of Edible Vaccine:

1. Selection of suitable, easy to grow, store and cost effective plant species
2. Selection of safe, stable antigene
3. Allergic and toxic issiues
4. Public perceptions
5. Vaccine regulatory authority and rules
6. Delivery and dosing issues

Fruit derived edible vaccine

Fruit is a part of a flowering plant that derives from specific tissues of the flower, mainly a single ovary. Fruits are most suitable for edible vaccine as there is no need to cook them. Cooking i.e. heat denatures the protein of edible vaccine. In fruits Banana and Papaya mostly used for edible vaccine production (Sharma *et. al.* 2011) [11]. Banana (*Musa acuminate*) is one of the earliest fruits used for plant transgenic programs. Papaya (*Carica papaya*) is a widespread tropical and semi-tropical fresh edible fruit. Banana and Papaya are inexpensive, grow quickly. widely grown in developing countries, containing high amount of Vitamin ' A'. Also Bananas are sterile so the genes don't pass from one banana to another. A research showed that promoter MaExp1 could be an important tool for expressing foreign proteins (vaccine) in banana fruit at the time of ripening (Hassler, 1995) [21]. The disadvantage of banana as edible vaccine is that it Spoils rapidly after ripening and contains very less protein.
Ideal edible vaccine should be affordable, having long lasting humoral and cellular immunities, Nontoxic and non-pathogenic, very low level of side effects, contaminate the environment, don't cause problems in individuals with impaired immune.

Advantages of fruit derived edible vaccine

1. Economical in mass production and transportation.
2. Don't need to cook
3. Heat stable, eliminating the need for refrigeration as compare to conventional vaccine.
4. Enhanced compliance in children.
5. Possible production of vaccines with low costs
6. Reduced need for medical personnel and sterile injection conditions.
7. Storage near the site of use.
8. Ease of administration.

Constraints of Edible Vaccine

1. Development of immune tolerance to vaccine peptide or protein.
2. Consistency of dosage form fruit to fruit, plant-to-plant, and generation-to-generation varies
3. Stability of vaccine in fruit is not known.
4. Dosage of vaccines would be variable.
5. Selection of best plant is difficult.
6. Cooking the food might weaken the medicine present in it.
7. Palatability is also a critical problem
8. Not convenient for infants.
9. Need to develop distinguish characters between 'vaccine fruit' and 'normal fruit'.
10. Acceptance of GM crops.

Applications

Large numbers of clinical trials are being carried out to validate the potential of edible vaccine. Edible vaccines are being developed for number of human and animal infectious disease like hepatitis B, cholera, measles, FMD etc. They may also help to suppress auto immunity diseases like type-I diabetes (Prakash, 1996) [37]. Prodigene a biotech company from USA has a patent for edible vaccine against Hepatitis B disease, University of Yale has a patent for Vaccine against invertebrates like insects, arachnids, helminthes etc. (Waghulkar *et al.* 2010) [52]. Foot-and-mouth disease (FMD) is one of the most contagious viral diseases of wild ruminant and domestic animals. The causative pathogen is FMD virus (FMDV). FMDV is a single stranded, positive-sense RNA virus, possessing four capsid proteins VP1, VP2, VP3 and VP4. The VP1 protein is the critical determinant for vaccination against FMD with the induction of VP1-neutralizing antibodies required for immunity. Studies have shown the potential of using VP1 capsid protein as a subunit PMV candidate, in potato, tobacco, and tomato (Dus et. al 2002) [15]. Potato-based vaccine against hepatitis B have reported that the amount of HBsAg needed for one dose could be achieved in a single potato. Levels of specific antibodies significantly exceeded the protective level of 10 mIU/mL in humans (Domansky, 1995) [14].

Conclusion

Fruit as a carrier for edible vaccination have double benefit of creating immunization as well as treating malnutrition. It replaces painful vaccination procedures. Compare to conventional vaccine, fruit derived vaccine is needle free, appealing to children, low cost, can be stored near to site of use, safe, provide mucosal and systemic immunity. Fruit derived edible vaccine may lead to a future of safer and more effective immunization if significant challenges can be overcome.

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