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Asian Journal of Animal and Veterinary Advances

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Asian Journal of Animal and Veterinary Advances 6 (8): 860-862, 2011
ISSN 1683-9919 / DOI: 10.3923/ajava.2011.860.862

Revisiting the Science of Plant-based Vaccines; Reduction in Utilization of Conventional Animal or Bacterial Systems but Biosafety Concerns

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Plant-derived pharmaceuticals (biopharmaceuticals) seem to become a promising platform for human health care as the science of biotechnology came from studies on plants starting 1980s. Nowadays, the world of plant productions has been changed fundamentally particularly in the field of plant biotechnology. Induction of resistance to biotic and abiotic stresses, improvement of plant's physical traits, production of reagent proteins, high value pharmaceuticals and nutritionally enhanced crops are the most important concerns in this field.

Considering human health issues, particularly in developing countries, improvement in manufacturing of vaccines (lowering the cost and reducing the production time) appear crucial. The advantages of biopharmaceuticals are counted in terms of production scale and economy, product safety, ease of storage and low cost while challenges in terms of environmental and human biosafety still remain. However, despite the promised benefits, the commercialization of plant-derived pharmaceutical products is overshadowed by the uncertain regulatory terrain, particularly with regard to the adaptation of good manufacturing practice regulations to field-grown plants (Ma *et al.,* 2005).

Plant-made vaccines diminish the utilization of conventional animal or bacterial systems. A typical limitation to traditional oral vaccines is that the antigen can be digested in the stomach before there is an immunogenic response (Streatfield, 2006). Reduction of chance for contamination with animal pathogens is an outstanding point for plant-derived vaccines, since there are no known plant pathogens to have a deleterious effect on animals. Also, the vaccines will be not contact blood or culture products, which increases overall safety compared to microbial or animal cell culture (Kirk and Webb, 2005).

As Aliahmadi *et al.* (2006) reported, plant transformation is achieved by two main tools including stable plant transformation (stable integration of desired genes into the plant genome, either nuclear DNA or chloroplast DNA) and transient transformation of plants through infection of plants by modified plant viruses which have a desired gene.

In a recent review, Rybicki (2010) listed an extensive plant types and systems that have been used for expression of vaccine antigens including various *Nicotiana* spp., *Arabidopsis thaliana*, alfalfa, spinach, potatoes, duckweed, strawberries, carrots, tomatoes, aloe and single-celled algae. Proteins have been expressed in seeds of maize, rice, beans and tobacco, in potatoes, tomatoes and strawberries, in suspension cell cultures of tobacco and maize, in hairy root cultures and in transformed chloroplasts of a variety of plant species.

The first vaccine protein to be produced in any plants was the hepatitis B virus (HBV) surface antigen (HBsAg). A successful production of a mouse hybridoma-derived monoclonal antibody (mAb) in transgenic tobacco (*Nicotiana tabacum* L.) was reported 20 years ago. In terms of edible fruits and tubers, tomatoes have been engineered to express a variety of antigens, including rabies

virus glycoprotein, respiratory syncytial virus F glycoprotein, a hepatitis E virus surface protein, a Yersinia pestis F1-V antigen, a synthetic HBV/HIV antigen, Norwalk virus capsid antigen, hepatitis B virus surface antigen (HBsAg) and a synthetic polypeptide containing epitopes of the diphtheria, pertussis and tetanus (DPT) exotoxins, among others (Rybicki, 2010).

Escherichia coli (*E. coli*) heat labile toxin vaccine (to treat diarrhea) has been produced utilizing maize/potato reached phase I clinical trials (Ma *et al.,* 2005). To treat rabies, *Rabies glycoprotein* vaccine (viral vectors in spinach) experiences phase I trials (Yusibov *et al.,* 2002). Bock and Warzecha (2010) reviewed several antigens successfully expressed in tobacco (plastid). These antigens target various diseases caused by viruses and bacteria.

In 2007, significant progression has been made in the area of host plant engineering. Tobacco and duckweed engineered in a way to have a more human-like glycosylation machinery using either RNA interference or by expressing a human or chimeric β-1,4-galactosyltransferase. Therefore host plants might express recombinant proteins that are essentially devoid of xylose or fucose residues and as a consequence are more human-like and safer (Gleba *et al.,* 2007).

Transgenic potato tubers have been used to produce *E. coli* heat-labile enterotoxin (LT-B), Norwalk virus coat protein, rabbit haemorrhagic disease virus (RHDV) VP60, HBsAg, a combination cholera/*E. coli*/rotavirus vaccine, human papillomavirus E7 and L1 proteins and Newcastle disease virus envelope among many others (Rybicki, 2010).

HbsAg produced in both transgenic lupins and lettuce elicited specific antibodies in mice and humans, respectively; sunflower seed albumin produced in lupin has been tested as an anti-allergen vaccine; the small surface antigen of hepatitis B virus (S-HBsAg) has been produced in transgenic yellow lupin calli or tumours. The most notable achievement for this sort of expression for human vaccines, however, was probably the demonstration that measles virus haemagglutinin (MV-H) protein could be successfully expressed in transgenic lettuce and was immunogenic in mice (Rybicki, 2010).

E. coli LT-B toxin subunit assembled correctly in maize, was functional and protected orally-immunized mice against bacterial challenge. It has been demonstrated that a pea (*Pisum sativum*)-RHDV CTB:VP60 chimaeric protein protected rabbits against lethal challenge (Rybicki, 2010).

In a review, the total costing for plant production estimated 68% of the costing for conventional production (Rybicki, 2009). Another report confirmed that the cost of vaccine production per gram differ ranging from 150$ in mammalian (CHO) cells to 0.05$ in transgenic plants.

A missing point of the study by Aliahmadi *et al.* (2006) might be citing the risk and disadvantages of plant-derived pharmaceuticals beside the advantages. Plant based vaccines might impact on the environment and on human health. Risks to the environment include gene transfer and exposure to antigens or selectable marker proteins. Risks to human health include oral tolerance, allergenicity, inconsistent dosage, worker exposure and unintended exposure to antigens or selectable marker proteins in the food chain (Kirk *et al.,* 2005).

Recent year's studies confirm that plants are potentially very good source of future drugs in various aspects (Hasani-Ranjbar *et al.,* 2009, 2010; Momtaz and Abdollahi, 2010; Rahimi *et al.,* 2010) but this needs better studies to discover the composition of herbs and much better national research strategies. A potential application of plant biotechnology might be referred as the relation between antioxidant capacity of a plant and its susceptibility for being a candidate for vaccine production. Tomato which is frequently used as a vaccine production system (with a balanced mixture of minerals and antioxidants) sights as a great candidate. Several research projects have reported the usage of tomato plants as a source of antigens for hepatitis B and E, cholera,

respiratory syncytial virus and rabies virus. Another study has developed a transgenic tomato producing acetylcholinesterase which is needed to counteract organophosphate poisoning. Plants may be used to produce plantibodies, or plant-derived antibodies and tomato may also be a candidate plant for that use (Dalal *et al*., 2006).

Important elements for successful performance of plant biotechnology may be listed as follows: improvement of national biotechnology policy; adequacy of facilities and equipments; cooperation between universities, privet sectors and government agencies; biosafety regulation for "gene revolution"; conservation of natural resources; adaptation of technology from developed countries to local condition and development of communication systems. In conclusion, as reported by Aliahmadi *et al*. (2006), the science of plant based vaccines needs revisiting.

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