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Plant as Biofactories for Production of Therapeutically Important Compounds

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Plants are key hosts for manipulation of its cell machineries to produce therapeutically important compounds for the benefit of mankind. The production levels of recombinant proteins in plants are capable of meeting almost unlimited demand. Transgenic plants offer huge advantages for pharmaceutical protein production because plants can be grown on a larger agricultural scale and the protein products can be processed from them for various applications, more particularly for the therapeutic use.This technique relies on genetically modifying plants using established gene transfer methods for protein expression. Transgenic plants posses advantage as cost effective system for large scale production of producing safe recombinants (antibodies, enzymes, vaccines, growth factors, etc.). This can be met by integrating protein engineering tools, use of expression technologies, and large scale cultivation of plants and downstream processing of the biopharmaceuticals.

Plants can successfully carry out post-translational modifications for genetically diverse proteins and offers flexibility in bio production and also addresses limitations with respect to the scale of production, product safety, cost and regulatory challenges (Buyel, 2019). Now more than 250 biopharmaceutical products are already available in the market, which includes therapeutic enzymes, antibodies and drugs derived from antibodies, cytokines/growth factors, hormones,and bulk blood products, vaccines, prophylactic antibodies and their derivatives used during diagnostics. Recombinant protein production in host cell systems other than use of plants is majorly constrained by the cost of production and also is influenced by variety of other factors.

Plant as Biofactories

Plants are used for the production of recombinant proteins for several decades, however there were several hurdles for acceptance of it as expression system compared to the microbial production systems due to its usage as food or feed sources as part of the human food chain. The first plant-based product commercialized was "Elelyso" by Protalix Biotherapeutics for the treatment of Gaucher's disease in 2012 (Panya and Mohanty, 2015).

For the accomplishment of the molecular pharming methodology, by selecting the right plants for the technologies is an essential factor (Makhzoum *et al.*, 2014). Plants are being considered by researchers and industrialists as the most likely least expensive production hosts in their research towards cheap and effective expression methods for the manufacture of regenerative therapies.

Use of plants for production of high-value recombinant proteins ranging frompharmaceutical therapeutics to non-pharmaceutical products such as vaccines, antibodies,enzymes, growth factors, agriculturally important proteins and cosmetic ingredients has made dramatic changes over years and has led to a major paradigmshift in the pharmaceutical sector. A comprehensive list of the plant derived biopharmaceuticals is listed in Table 1.

Table 1.Plant derived biopharmaceuticals

Engineered Host plants	Category	Product	Application/comments
Tobacco	Protein	Growth hormone	First human protein synthesized from plants
	Antigen	Hepatitis B virus - antigen	1st vaccine used to expressed in plants
	Antibody	Secretory immunoglobulin A	Secretory antibody expressed in plant
	Protein	Human serum albumin	First full-size native human protein
	Protein	Erythropoietin	First protein produced in tobacco suspension cells
	Antibody	Single-chain Fv antibody fragments	Non-Hodgkin's lymphoma
	Antibody	Non-Hodgkin's lymphoma	Dental caries
	Microbicide	Cyanoverin-N	HIV
Spinach	Vaccine	Rabies glycoprotein	Rabies
Lettuce	Vaccine	Hepatitis B virus surface antigen	Hepatitis B
	Protein	Ebola virus - 6D8	Ebola virus
Rice	Dietary	Lysozyme, Lactoferrin, Human serum albumin	Diarrhoea
	Protein	α-Interferon	The first human pharmaceutical protein produced in rice
	Protein	Japanese encephalitis virus (JEV) envelope protein (E)	Japanese encephalitis virus
Maize	Vaccine	*E. coli* heat-labile toxin	Diarrhoea
	Therapeutic enzyme	Gastric lipase	Cystic fibrosis, pancreatitis
	Dietary	Lactoferrin	Gastrointestinal infection
Potato	Vaccine	Norwalk virus capsid protein	Norwalk virus infection
	Protein	Spike (S) protein	Infectious bronchitis virus
	Vaccine	Hepatitis B virus surface antigen	Hepatitis B virus (HBV)
Tomato	Protein	Lactoferrin	Antimicrobial activity
	Vaccine	Rabies virus glycoprotein	Edible vaccine expressed in edible plant tissue
Arabidopsis	Dietary	Human intrinsic factor	Vitamin B12 deficiency
Safflower	Hormone	Insulin	Diabetes
Tobacco	Antibody	P2G12	Neutralises
Carrot	Protein	Heat-labile toxin B subunit (LTB)	Enterotoxigenic*E.coli*

Strategies for production of biopharmaceuticals:

- Stable transformation, which involves the nucleus and Transformation of the plastid,
- Transient transformation incorporating virus- and Agrobacterium-mediated techniques Magnification system, and
- Cell suspension method.

For production of biopharmaceuticals, the technology used are production of stable nuclear transgenic plants, transplastomic plants, transient expression using a plant virus (Tobacco Mosaic Virus) and transient expression via *Agrobacterium* infiltration (Floss *et al*., 2007).The gene of interest needed to make the pharmaceutical is transformed using the plant virus or *Agrobacterium* or into plant genome directly using well established plant transformation methods and the products harvested, processes and purified for extraction of biopharmaceuticals (Fig.1).

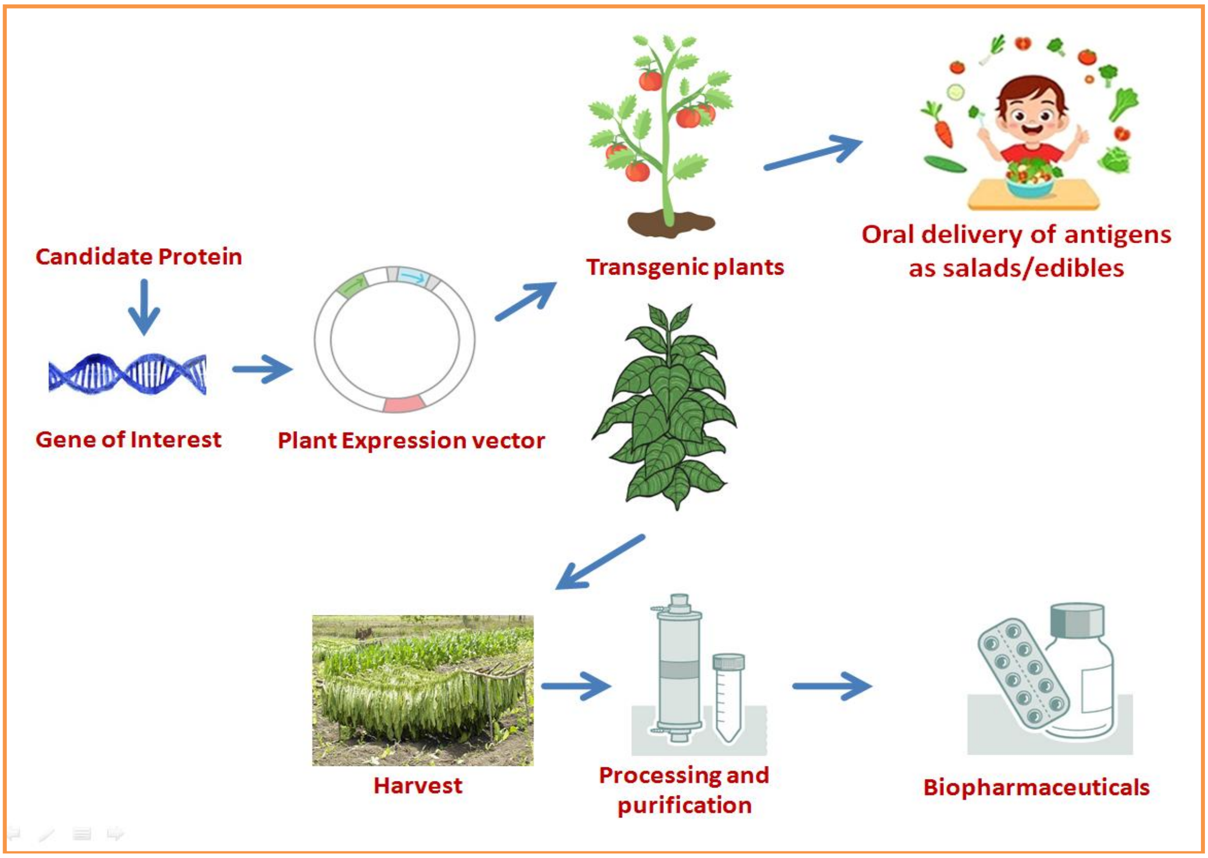

Fig. 1. Strategies for production of biopharmaceuticals in plant systems

Advantages of Plants Expression Systems

- Established cultivation practices
- low expenses of production
- Plants do not carry pathogens that might be dangerous to human health
- ability of the plants to assemble complex proteins with eukaryotic-like post-translational modifications (PTMs).
- rapid mass production of recombinant proteins
- easy storability and transport to even remote areas since the seeds and fruits serve as sterile packaging containers for the valuable therapeutics

Conclusion

The major objective of molecular pharming is to generate large quantities of safe and secure recombinant protein at affordable cost. Using plants as Biofactories helps to produce them at a cheaper price and serves as better alternative source of medicines in both industrialized and developing countries. Like any technology, plant molecular pharming as an application of plant genetic engineering may have possible risks, concerns, and other issues. Future advancements in this field depends on how well clinical studies go and whether they are approved for usage in humans to exploit the fullest potential of this system.

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