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Molecular Farming in Plants: A Novel Biotechnological Tool in Field of Medicines

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Introduction:

Molecular farming is a biotechnological program that includes the genetic modification of agricultural products to produce proteins and chemicals for commercial and pharmaceutical purposes. Recombinant protein and other secondary metabolite production in plants is referred to as "plant molecular farming." For this technology to work, plants must undergo a genetic transformation that can be achieved through both stable gene transfer techniques, such transferring genes to chloroplasts and nuclei, and unstable transfer techniques, like viral vectors. A growing need for biomedicines has also been accompanied by high costs and ineffective production methods (bacterial, microbial eukaryotes, mammalian cells, insect cells, and transgenic animals).Due to several advantages, including the safety of recombinant proteins (antibodies, enzymes, vaccines, growth factors, etc.), and their potential for mass-production at low cost, transgenic plants have drawn a lot of attention as the bioreactors of a new generation. Molecular farming can offer efficient solutions for the current growing need for the biomedicines. Plants provide an inexpensive and simple system for the production of valuable recombinant proteins on large scale, and compared to the other production systems, they have numerous advantages in terms of economy, safety, and applicability. Recombinant proteins could be produced in nearly infinite quantities through molecular farming in plants and used in medicine and the life sciences as diagnostic and therapeutic agents.

Background of molecular farming:

Molecular farming activity has existed since the first higher plant was successfully transformed (Fraley *et al.* 1983), One of the earliest marker genes that scientists have used in developing transformation systems in plants, aids (Jefferson *et al.* 1987), is now a molecular farming product (Kusnadi*et al.* 1998; Witcher *et al*.1998). The first report of human antibodies produced in plants was by During (1988) and was expanded to include secretory antibodies by Hiatt *et al.* (1989). Hood *et al.* (1997).'s description of the creation of avidin, an egg protein with a number of crucial characteristics, was the first account of a protein being created in plants with the specific intention of extracting, purifying, and selling that protein. Aprotinin, one of the first medicinal proteins to be generated molecularly in plants (Zhong *et al.* 1999), may soon be applied to patients' wounds to help them heal and to inhibit the body's inflammatory response during surgery.

Molecular farming:

Molecular farming is the production of recombinant pharmaceuticals outside their natural source. By definition, molecular farming is preceded by identification of a protein with a desirable therapeutic or diagnostic activity, its protein and DNA sequencing and finally its expression in a heterologous host.

A classic example of molecular farming in microbes is the expression of recombinant insulin in bacteria.

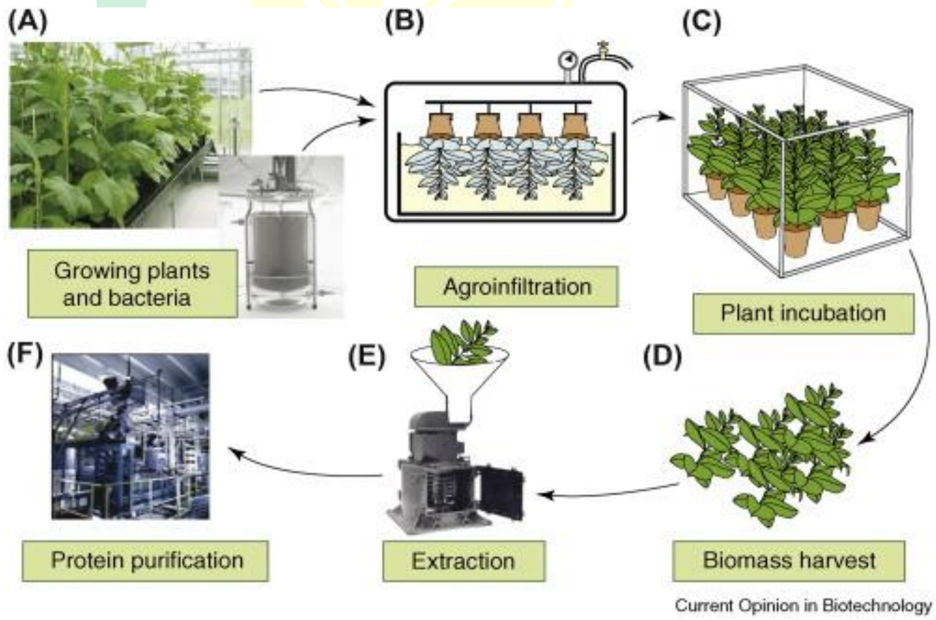

Illustration of Process of Molecular farming

Explanation of process of Molecular farming:

- The recombinant protein/antigen expression cycle takes 6–10 days starting with agro infiltration of grown plants and Agrobacterium culture.

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- Agroinfiltration is accomplished by submerging plants in bacterial culture harboring plasmid vectors coding for gene of interest and subjecting them to vacuum pulse to force the bacterial culture in,
- Plants are incubated for several days.
- and harvested,
- By strictly controlled protocol designed to prevent the release of genetically engineered bacteria into the environment. Subsequently, the extraction of recombinant proteins is carried out,
- And the purification to make the recombinant drug or vaccine.

Molecular farming systems:

Currently, there are four methods for extracting protein from plants:

- Stable nuclear transformation of a crop species that will be grown in the field or a greenhouse
- Stable plastid transformation of a crop species
- Transient transformation of a crop species
- Stable transformation of a plant species that is grown hydroponically such that the trans-protein is secreted into the medium and recovered.

Stable nuclear transformation:

It is the most common method and produced all of the products available in the marketplace today. This system requires a method for transferring the foreign genes into the plant cells, usually using *Agrobacterium tumefaciens* or particle bombardment, in which the genes are taken up and incorporated into the host nuclear genome in a stable manner.

Advantages:

- When performed in a crop species such as grains, the protein product is normally accumulated in the seed, which is then harvested in a dry state and stored until processing can be accomplished.
- Large acreage can be utilized with the lowest possible cost.

Disadvantage:

Some grains, such as corn, have the potential to cross with native species or food crops. There are technologies that will prevent out crossing, e.g., mechanical detasseling, or genetics-based male sterility (GMS). Such technology generally reduces the cost advantage of the system due to higher manual labor requirements, lower yields, and less effective genetics.

Plastid transformation:

The system for plastid transformation was first described by Svab*et al.* (1990) using tobacco. The plastid transformation technology was birthed as a result of the quest for low cost, safer and more flexible scale up expression system than the established system that use bacterial, fungal and animal cell as production platforms for recombinant proteins, especially pharmaceuticals proteins.

Advantages: Protein expression levels exceeding 40% on a dry weightbasis have been reported when tobacco chloroplasts weretransformed.

Disadvantages: As with any fresh tissue molecular farming system,

- Protein stability over time will change even with refrigeration.
- Extraction and purification must be performed at very specific times following harvest.
- Large volume products and edible vaccines would not appear to be feasible using this system.

Transient crop species transformation: This approach depends on recombinant plant viruses like tobacco mosaic virus (TMV) being able to infect tobacco plants and then temporarily express a target protein in the plant tissue.

Advantages:

- TMV is easily genetically manipulable, and the infection process is quick.
- It takes a few weeks to obtain small amounts of the target protein.
- It is probably the best solution for a lot of specific proteins that are required in small doses.

Disadvantages:

- It's probably not appropriate for any protein that is required in large (kg) quantities.
- The product needs to be handled right away because storing it will deteriorate the plant tissue.

Stable transition of a hydroponically cultivated plant species:

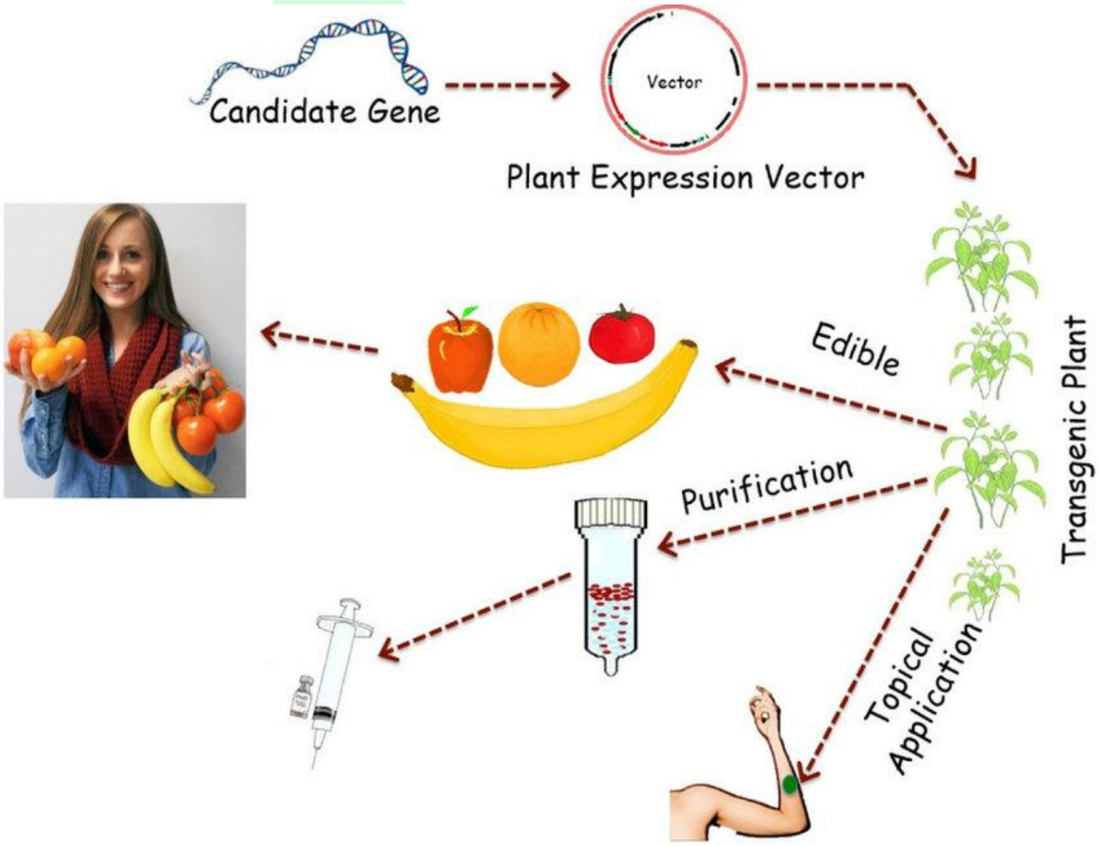
This method involves growing transgenic plants hydroponically such that the intended product can be released as a component of the root secretions into the hydroponic medium. The transgenic plants have a gene that codes for the target protein.

Advantages:

- Because hydroponically grown plants are enclosed in a greenhouse environment, there is less concern about accidental environmental release.
- Because there is little to no protein contamination and no tissue degradation is necessitated, it is much simpler to purify the desired product.

Disadvantages:

- Making substantial (kg) amounts of any protein product is probably not feasible.
- The cost of operating greenhouse/hydroponic facilities is somewhat high.



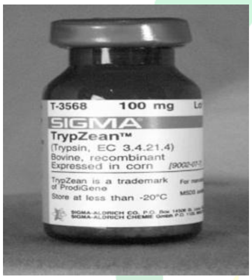
Diagrammatic illustration of the process of plant molecular farming

Explanation:

First of all gene of interest is isolated, then using relatively routine molecular methods placing the gene of interest into the plant expression vectors and transforming into the plants. The transgenic plants are produced, which leads to the production of plant derived edible human vaccines, using leafy plants or fruits, finally products are make available to the humans for consumption.

Classes of proteins within molecular farming:

- **Parental therapeutics and pharmaceutical intermediates:** This group includes all proteins used directly as pharmaceuticalsalong with those proteins used in the makingof pharmaceuticalsincludes products such as thrombin, collagen, trypsin and aprotinin.
- **Industrial proteins-enzymes:** This group includes hydrolases, encompassing both glycosidasesand proteases.
- **Monoclonal antibodies:** This group includes all antibody forms (IgA, IgG, IgM,secretory IgA, etc.) and antibody fragments (Fv).
- **Antigens for edible vaccines:** Specific protein antigens can be produced in plants thatwill induce a humoral immune response when eaten by ananimal or human.



TrypZean, (a corn-derived recombinant bovine trypsin product), is the first large-scale plant molecular farming product to reach the market.

Advantages of molecular farming in plants:

- Significantly lower production costs than with transgenic animals, fermentation or bioreactors.
- infrastructure and expertise already exists for the planting, harvesting and processing of plant material.
- plants contain no known human pathogens (such as prions, virions, etc.) that could contaminate the final product.
- higher plants generally synthesize proteins from eukaryotes with correct folding, glycosylation, and activit.
- plant cells can direct proteins to environments that reduce degradation and therefore increase stability.

Conclusion:

The aim of molecular farming is to produce large quantities of active and secure pharmaceutical proteins with lower prices. With the scientific advances in the field of bio-technology, gene transfer methods in plants have considerably developed. These transgenic plants in comparison with other microbial and animal expression systems have various advantages in terms of easy production, cost, safety etc. for producing pharmaceutical biomolecules. So far, lots of valuable pharmaceutical proteins and antibodies have been produced by the help of this method, which remarkably has helped the treatment of patients especially in developing countries where the production and preservation costs of such medicines cannot be afforded.