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Plant Molecular Farming: Harvesting Green Bioreactors in the quest for affordable therapeutics against Diabetes

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ABSTRACT

Plant molecular farming representing an innovative and cost-effective platform, offers a cheaper and highly adaptive strategy for manufacturing biologics in plant systems. Genetically engineered plant systems as bioreactors serve as a new generation biopharmaceutical source considering its advantages. The essence of this technology is a successful genetic transformation in plant either through stable gene transfer (nuclei and chloroplast) or through viral vectors. Despite its potential, several biosafety issues entail concerns like transgene diffusion, recombinant protein toxin accumulation and ethical considerations like contamination of food chain accompany its deployment and generate the need for investigative production of biologics. This review explores the methodology, applications and challenges that come with the production of recombinant protein using plant source for the disease that poses as a global implication on the wellbeing of individuals, namely diabetes.

KEYWORDS: Molecular farming, transgenic plants, recombinant protein, Plant bioreactors, diabetes. **KEYWORDS**: brain gymnastics, psychological performance, primary school girls.

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INTRODUCTION

Plant Molecular farming has emerged as an upcoming and transformative biotechnological platform for the production of high value recombinant animal proteins which include therapeutic and commercial enzymes, vaccines and antibodies offering a promising alternative to traditional microbial or mammalian cell-based production platforms. Since its inception in 1980s marked by the primary success of synthesizing recombinant human growth hormone- insulin in *Escherichia coli* and later advancing in plant-based expression system by producing recombinant protein in 1986 and 1989 respectively[1], [2], the field has rapidly evolved. The enterprise expanded into both research and commercial domain by the synthesis of first recombinant protein, Avidin produced by transgenic maize[3] and the synthesis of anti-cancer antibody Herceptin - produced in cells of mammalian origin (the ovarian cells of the Chinese hamster (CHO cells). The relevance of this industry is significant considering the global health inequities. A vast majority of low- and middle-income countries in the stage of development cannot afford the medical treatment from the existing methods owing to their high manufacturing cost and complex storage requirement. Plant based systems offer a compelling and inexpensive solution through high scalability, low production cost and reduced risk of contamination with human pathogens, hence suitable for manufacturing pharmaceuticals intended for a widespread use in resource constrained settings. Presently the major focus of this emerging technology is pharmaceutical products and healthcare applications but the scope of molecular farming can also be extended in the production of food and feed additives, industrial enzymes, biopolymers and investigative proteins, Human serum proteins, antibodies, biomedicines, vaccines hormones and enzymes.

Characteristics	Bacteria	Mammalian cell culture	Transgenic plants	Plant cell culture
Production cost	Average	High	Low	Low
Post-translational modifications	No	Yes	Yes	Yes
Function	High	Average	High	High
Protein stability	Yes	Yes	Yes in seeds	Yes

Fig 1: Comparison of different expression systems for recombinant protein production

However, this technology ventures into intricate religious and ethical terrains as the integration of animal protein genes into plant system raises ethical, regulatory and environmental concerns necessitating public dialogues and biosafety assessments. It also poses novel challenges and brings unique regulatory concerns to domestic and international markets which includes public health concerns related to animal proteins produced in plants, unintended allergens or cross contamination of unwanted proteins highlighting the need re-evaluating the transgenic product policies aiming to foster an inclusive discussion which navigates the ethical, religious, and environmental implications of integrating animal proteins into plant-based systems. The aim of this study is to review and detail the process, challenges and future prospects of molecular farming with particular emphasis on its potential to revolutionize therapeutic strategies to eradicate diabetes- a disease with rapidly increasing global prevalence: its challenges, biosafety and public acceptance.

3. Strategies employed for plant transformation

3.1 Permanent expression systems

This strategy is employed to permanently ingratiate the gene of interest or nominated genes in the plant genome. This can be employed by three methods.

a. Stable nuclear transformation

Stable nuclear transformation refers to integration of foreign gene in the nuclear genome of plant resulting in variation in the genomic structure and subsequently alteration of expression of transgene. It is one of the most common methods. This system required transferring foreign gene in 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. This considered to have considerable potential in cereals however long production cycle along with cross breeding with natural species have limited the application of this method[4], [5].

b. Stable plastid transformation

Plastid transformation prevents the transgene escape through the process of amphimixis as plastid inheritance is maternal by nature in majority of the species hence reducing environmental concerns [6].

c. Plant cell suspension culture

Plant cell suspension culturing essentially removes the cell wall of plant cell. Gene transfer is obtained via protoplast or suspension culture. This process has a major advantage of reducing the heterogeneity in proteins and sugar (N-glyans) as the cell type and size are uniform along with an easier and economical downstream processing [7], [8]. Despite its advantages, it is not deemed as an optimal choice since its usability of recombinant protein is constrained by enhanced proteolytic activity in stationary phase [9].

d. Stable plant transformation that is grown hydroponically

Hydroponic development of transgenic plants allows the release of desired protein product as part of the root exudate into the hydroponic medium.

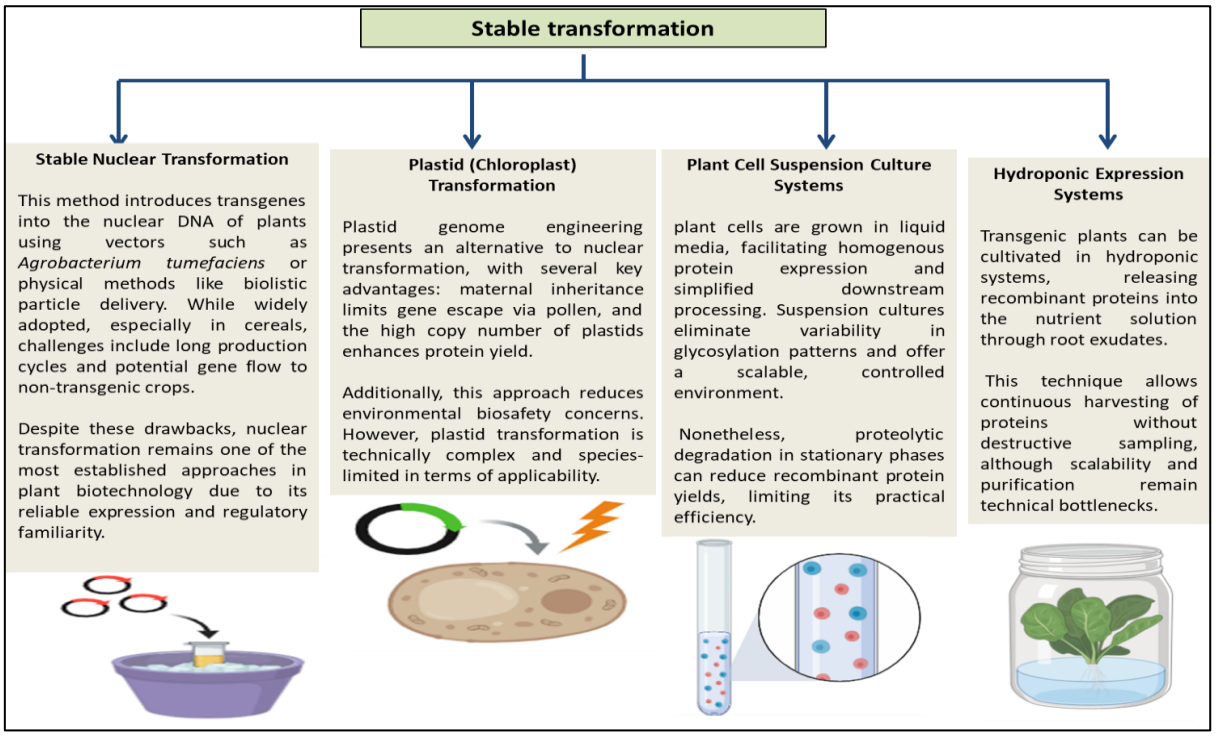

Figure 2: Methods of stable expression systems along with its recent accomplishments

3.2 Transient expression systems

Transient production of transgenic proteins are considered to be the quickest systems for plant molecular farming and mainly utilized technology for verifying expression constructs and validate protein expression [10], [11]. This can be employed by three methods:

a. **Agrobacterium Mediated transformation method**: This method facilitates the transfer of T-DNA to a high percentage of cells where transgenes can be expressed without a stable transfer. This method is greatly exploited for the production of biomedicines [12].

b. **Viral Infection methods**: this method mainly is reliant on the capacity of plant virus (eg: TMV; X-potato virus). These vectors act as a vector to convey foreign genes into plant genomes without plant genome blending[13].

e. **Magnifecation system**: this method significantly increases Transgene proliferation by removal of coat proteins of non-competitive viral strains and inducing a systemic delivery of derived viral vectors to all plants using Agrobacterium mediated transformation as the medium of infection.

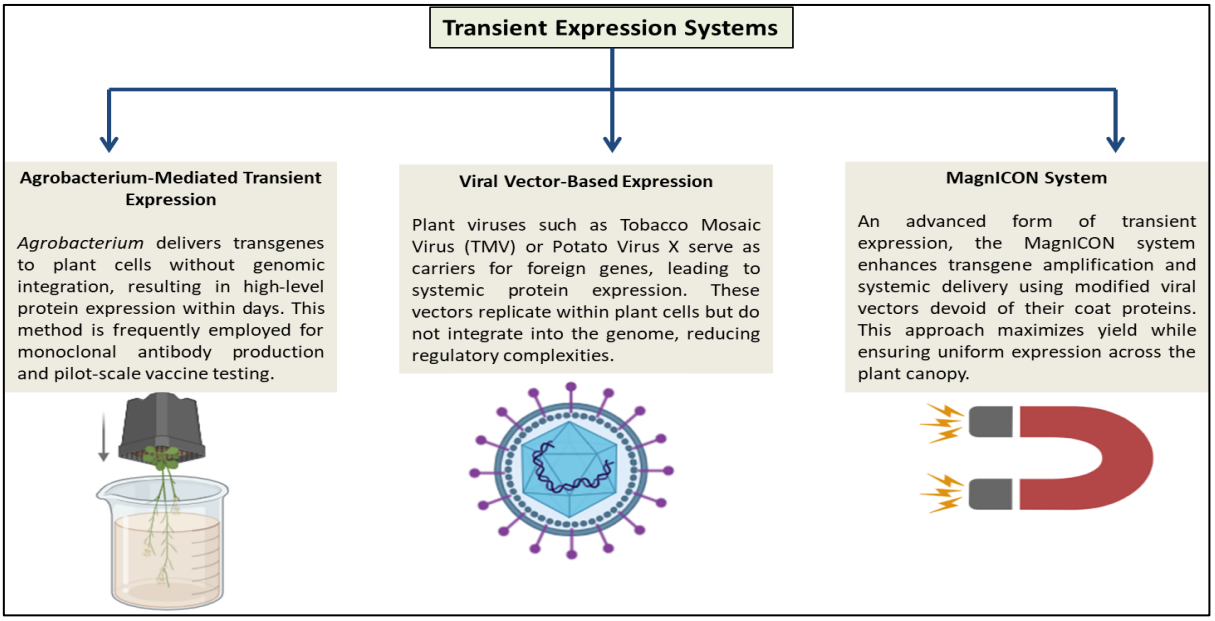

Figure 3: Methods of transient expression systems along with its recent accomplishments

Considering choice dependent factors lie protein complexity, urgency of production, regulatory pathway and downstream processing, stable and transient systems equally contribute significantly to Molecular farming.

4. Procedure and considerations of molecular farming

4.1 Selecting appropriate host plants

Major economic factor to select an appropriate plant host[14].

1. High potential of Transformation and regeneration.
2. Ease of protein extraction.
3. Biomass yield.
4. Ease of transport.
5. Maintenance cost.
6. Availability of organization workers.
7. Duration of production cost and Edibility.
8. Storage characteristics and cost.

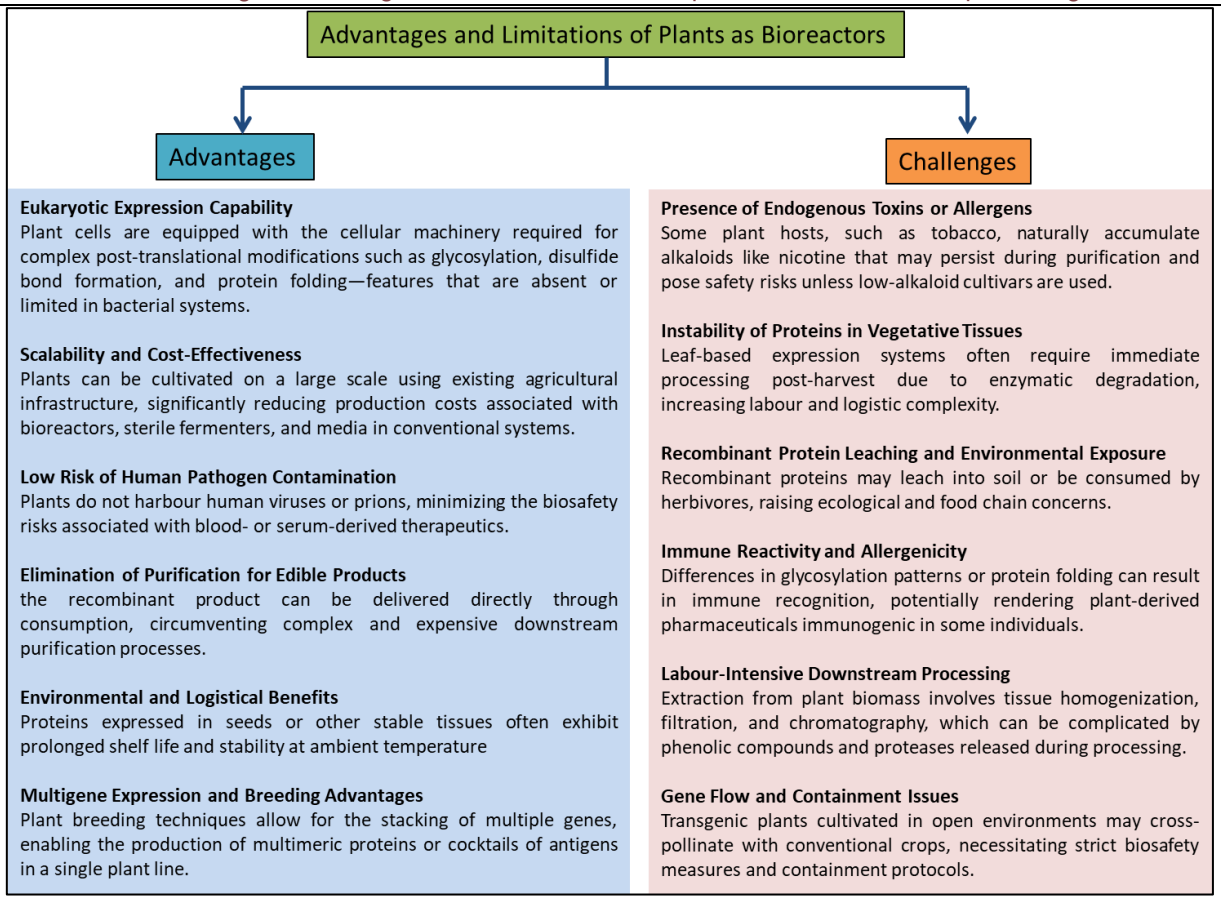

Figure 4: Advantages and Limitations of Plants as Bioreactors

4.2 Seed based expression of protein

- This method is considered more ideal as it neither affects the growth or development of the plant.
- Does not require immediate processing like freezing after harvest for long term preservation of protein as it is required in leaves [15].
- Storage is easy and cost effective.
- High rate of biomass yield (Cereals).
- Self-pollinating legumes (soy, peas) offer greater protein accumulation (20-40%) [16].

4.3 Leafy crops: Tobacco, alfalfa, soybean, lettuce

- Mature and standardized gene transfer and expression technology.
- Higher biomass yield.
- Higher and rapid scale up owing to prolific seed production.
- Higher potential of tobacco for transformation and regeneration.
- Low alkaloid varieties of Tobacco can be used for the production of pharmaceutical proteins.
- Alfalfa and soybean have reduced need of chemical fertilizers.
- Alfalfa and soybean- mainly utilized to produce recombinant antibodies.
- Soybean- used to produce Aspergillus phytase.
- Lettuce- production of recombinant vaccine.

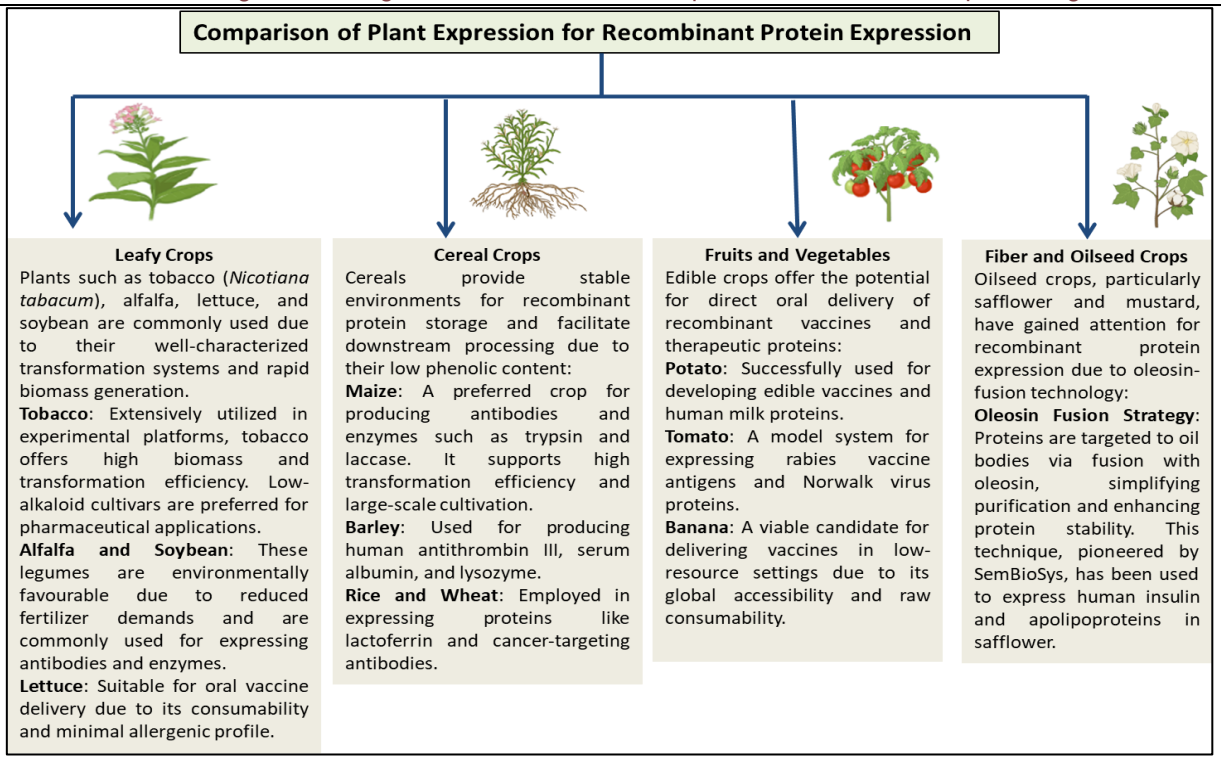

Figure 5: Plant Expression systems for Recombinant Protein Expression

4.4 Cereals and legumes

- Recombinant protein in seed allow long term storage at ambient temperature
- Seed drying, processing is easier and more robust for recombinant protein
- As cereal seeds lack phenolic compounds, it increases the efficiency of downstream processing
- Maize: considered the main commercial production crop for molecular farming for the production of recombinant antibodies and pharmaceutical enzymes like trypsin, aporotinin and laccase owing to
- High biomass yield
- Standardized transformation, in vitro manipulation and regeneration protocol
- Ease of scaling up
- Barley: Recombinant proteins production: Human antithrombin III, α1 antitrypsin, lysozyme, serum albumin and lactoferrin
- Rice and wheat: Human lactoferrin, recombinant antibody against carcinogenic antigen generated.

4.5 Fruit and vegetables

- Can be consumed either raw or partially processed.
- Suitable candidates for the production of recombinant subunit vaccines and antibodies for topical passive immunotherapy.
- Potatoes: widely utilized for production of plant derived vaccines, human milk proteins and antibodies
- Tomatoes: used to produce first plant derived rabies vaccine
- Lettuce: recombinant vaccines
- Bananas: recombinant vaccines

4.6 Fibre and oil crops:

- Production of recombinant protein cost is lower
- Fibre and oil interfere with the downstream process. The exception is the oleosin-fusion technology developed by SemBioSys Genetics, in which the targeting of recombinant proteins to oil bodies can be used to facilitate purification. This technology is majorly utilized in safflower and mustard[17], [18].
- Olesin fusion technology involves the fusion of the recombinant gene sequence to the sequence of a protein which expresses oil called olesin in safflower and canola which can be easily separated by the digestion of internalprotein followed by recombinant protein purification [19].

Molecular Farming provides an adaptable platform by leveraging versatile plant systems tailored to a specific protein allowing researchers to balance cost, yield, and processing considerations and also addresses Biosafety issues ultimately meet therapeutic needs.

5. Optimization of transgene expression and Protein stability

5.1 Promotors and regulatory elements.

It is fundamental to choose an efficient promoter for competent transcription of a transgene. The commonly used elements include:

- **a. Constitutive Promoters**
  1. *Cauliflower Mosaic Virus (CaMV) 35S* promoter: Widely employed in **dicots**, continuous robust expression
  2. *Maize Ubiquitin promoter*: effective in **monocots**, supports high level gene expression especially in cereal crops.
- **b. Tissue Specific Promoters**
  a. Spatially restricted expression
  b. Expression can be achieved by using organ/tissue specific promoters. Eg: Tomato E8 promoters (fruit specific) for antigen expression in edible tissues increasing oral vaccine efficiency[20].

5.2 Translational optimization

Strategies applied to enhance translation of recombinant proteins are:

a. **Leader sequences**: To increase ribosomal efficiency, 5′ untranslated regions (UTRs) derived from viral RNAs such as Alfalfa Mosaic Virus (AMV) leader or Tobacco Mosaic Virus (TMV) **Ω**- Leader are useful to increase translational efficiency by enhancing Ribosomal Binding.
b. **Codon Optimization**: utilized to minimize translational stalling and enhacing protein output by associating the modified transgene with the codon usage preference of the host plant.
c. **Translational Initiation context**: To improve translational initiation process in both dicots as well as monocots, Kozak consesus sequences are incorporated (e.g., ACCAUGG) near the start codon.

5.3 Enhancing Transcript stability

a. **Matrix Attachment Regions (MARs):** DNA elements help tether the transgene to the nuclear matrix hence moderating position effects and enhancing stable transcription of the transgene.
b. **3′ UTR Engineering:** Incorporating 3′ UTR or AU-rich sequences evades degradation signals and aids to improve transcript half-life.
c. Mini chromosome Technology: This method allows site specific gene stacking without integration into native genomes, offering stability and supressed gene silencing.

5.4 Protein targeting and stability

The recombinant protein's intracellular fate relies on their stability and ease of its purification. To achieve the same, strategies employed are:

a. **Endoplasmic Reticulum (ER)**: Fusion of endoplasmic reticulum retention signals (e.g. SEKDEL) or signal peptides (e.g. γ-zein) mainly localize proteins to ER and hence simplifying the process of glycosylation and folding.
b. **Vacuole or storage bodies**: Protein storage vacuoles prevent degradation and facilitate accumulation of sequestered recombinant proteins.
c. Oil bodies (Oleosin fusion): Fusion of Oleosin enables lipid droplet localization in seeds enhancing protein protection and easing downstream recovery.
d. **Cystolic Retention**: Using protein inhibitors or by fusing protective C-terminal extensions resists degradation and helps protein stailization in the cytosol.
e. Chloroplast: The prokaryotic-like machinery of chloroplast supports high expression levels and its containment. It is suitable for protein expression that does not require glycosylation.

By strategically integrating molecular elements and targeting motifs into expression cassettes, it is possible to significantly enhance recombinant protein yield, integrity, and functional efficacy key determinants for the commercial success of plant molecular farming.

6. Glycosylation challenges and intracellular localization

These approaches have shown considerable success in producing functionally equivalent, human-compatible glycoproteins in plant systems.

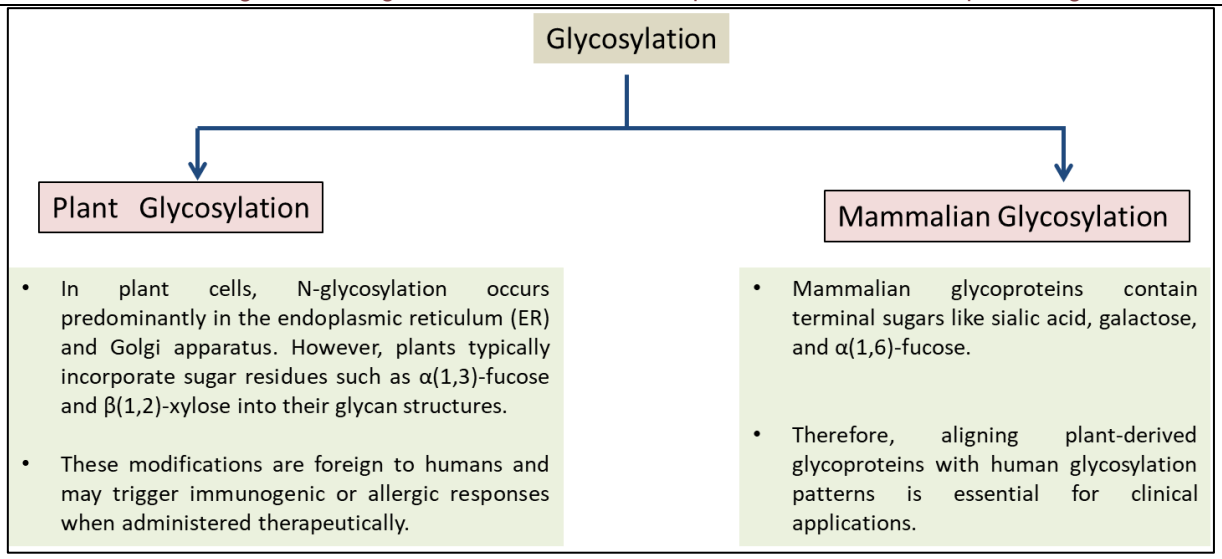

Figure 6: Difference between plant and Mammalian glycosylation

6.1 Strategies for Glycoengineering in plants

Several Glycoengineering strategies have been employed and have shown considerable success in producing functionally equivalent human Humanized Glycoproteins in plant system:

a. **Co-Expression of Human Glycosyltransferase**: introducing genes such as sialytransferase and β(1,4)-galactosyltransferase enables human type sugar residue to be added to plant derived proteins.
b. **Subdued endogenous plant Glycosylation enzymes**: Utilizing targeted gene silencing methods of plant specific fucosyltransferase and xylosyltransferase minimizes the addition of immunogenic residues.
c. **Subcellular targeting to ER**: Using SEKDEL helps direct proteins to the ER and hence limits the exposure of the protein to plant specific Golgi enzymes thereby producing less immunogenic glycan structures.

6.2 Intracellular Targeting and localization Tools for enhancing protein accumulation, folding and structure stability

a. **ER Targeting**: facilitates proper protein folding which is critical for therapeutic antibodies and enzymes as ER provides an oxidizing environment rich in molecular chaperons.
b. **Chloroplast Targeting**: it is ideal for proteins that do not require glycosylation. Chloroplast targeting yields high protein expression levels and minimizes proteolytic degradation.
c. **Vacuolar Sequestration**: Long term accumulation of targeting recombinant proteins especially in seed-based expression systems.
d. **Oleosin Fusion in oil bodies**: efficient recovery of proteins from oil rich tissues, protecting them from cytosolic proteases.
e. **Cytosolic stabilization**: Fusion of proteins with stabilizing cofactors such as cathepsin D inhibitors or protective sequences minimizes degradation and enhances recovery yields.

Molecular farming platform heavily relies on a thorough understanding of both plants Glycosylation methods and sub cellular localization strategies ensuring functional equivalence to mammalian derived therapeutics and enhance plant-based biopharmaceuticals translational potential.

7. Diabetes- Global Burden and its Epidemiological overview.

Diabetes mellitus (DM) has emerged as one of the most pressing chronic metabolic disorders of the 21st century [21]. It is the third highest cause of death in urban countries followed by cardiovascular diseases and approaching cancer mainly targeting the low- and middle-income countries which account for 75% of global diabetes cases. These regions often lack healthcare infrastructure, medication affordability, and cold-chain logistics, which further complicate disease management and prevention efforts. Diabetes has claimed 536.6 million lives within the age bracket of 20-79 and is predicted to affect 783.2 million lives by the year 2045 [22], [23]. (International Diabetes Federation, IDF). Characterized by chronic hyperglycemia resulting in defective insulin secretion, action or both, diabetes causes multiple organ failure over time and is associated with increased morbidity and eventual mortality [24].

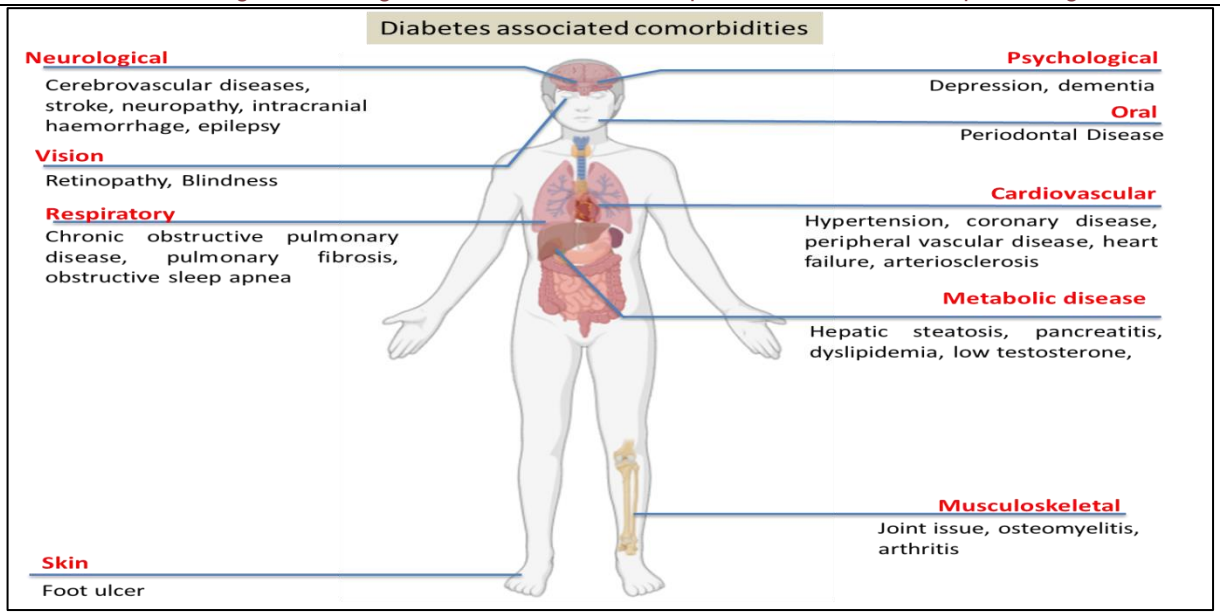

Figure 7: Diabetes associated comorbidities

8. Integration of Molecular farming in Diabetes therapeutics

The global epidemic named Diabetes necessitates a novel, scalable and cost-effective therapeutic solution. Molecular farming presents a favourable strategy for addressing the clinical, social and economic challenges associated with conventional diabetes treatments.

Plant molecular farming can be employed to produce several classes of biologics relevant to diabetes care:

8.1 Potential targets and recent case studies

a. **Recombinant human insulin**: early studies have already demonstrated successful expression of functional human insulin in plant tissues. Expression in seed-based platforms may enable oral delivery systems, bypassing the need of cold chain logistics and syringes offering a potentially low-cost alternative[25].
b. **Antibody based therapeutic**: To reduce manufacturing costs and production time, production of monoclonal antibodies manly targeting the inflammatory pathways allied with insulin resistance or beta cell destruction (especially Type I diabetes) using transient expression systems can be employed[26].
c. **Glucagon-like peptide-1 (GLP-1) and analogues**: Expression of GLP-1 (Receptor agonists playing key modulators of insulin secretion and glucose metabolism) analogs in edible plants like lettuce or tomato aiming enhanced patient compliance and accessibility has been proposed for oral delivery systems[27].
d. **Amylin and C-Peptide**: recombinant insulin can also co secrete peptides which can support research into combination therapies and offer a spectrum of new treatment modalities[28].

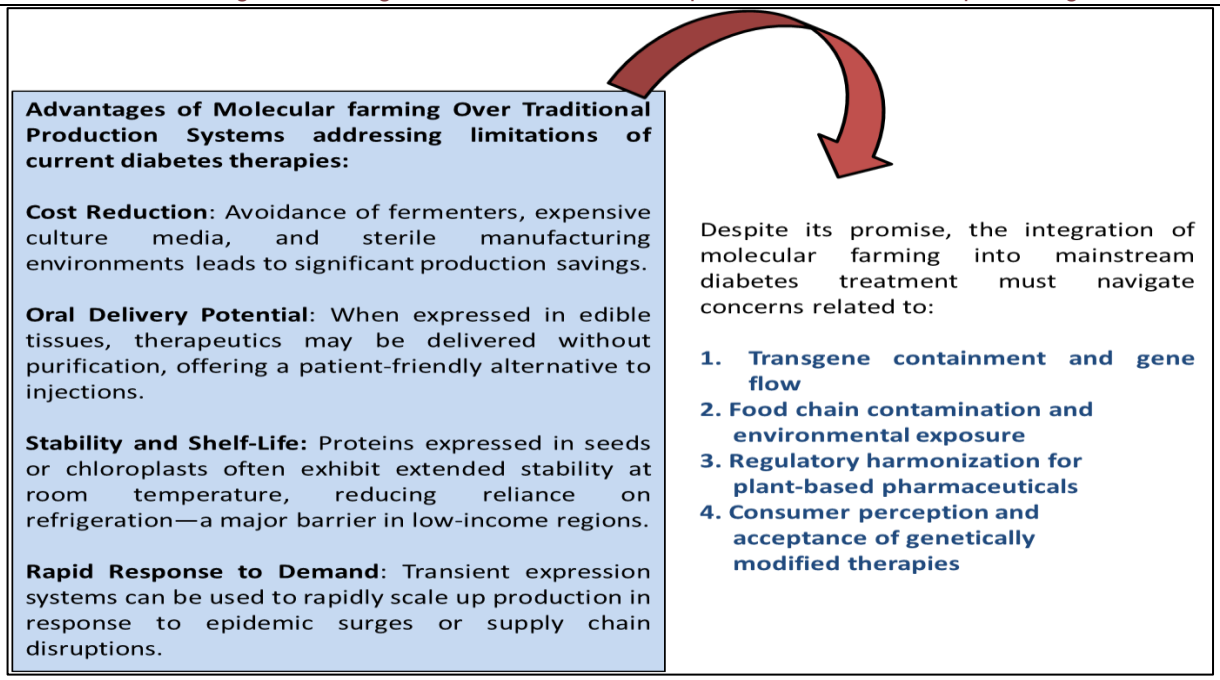

Figure 8: Advantages of Molecular farming over traditional production systems addressing biosafety concerns and public perception.

8.2 Recent Developments and Case Studies

- Expression of insulin-like peptides in *Arabidopsis* and *Nicotiana benthamiana* systems[29].
- Production of plant-based antibodies targeting diabetic retinopathy and inflammatory markers [30].
- Clinical testing of edible vaccines and protein formulations in lettuce and rice models, showing promising oral bioavailability[31].

Most of these approaches remain in preclinical or pilot scale; they form a solid groundwork for future translational efforts offering a sustainable route to equitable access to life saving medications. It aligns with the goals of World Health Organization seeking reasonable, decentralized health interventions owing to its ability to bypass the costly infrastructure needed for microbial and mammalian cell cultures. Since Regulatory frameworks for plant-based biopharmaceuticals are still immature, further sensitization and harmonization to secure consumer trust is required by standardizing biosafety assessments, labelling policies and public outreach programs.

Future Prospects

As plant molecular farming continues to evolve, its role in addressing global health challenges including diabetes is poised to expand significantly. Advances in genetic engineering, synthetic biology, and regulatory science are accelerating the transition of this technology from proof-of-concept to practical, market-ready solutions.

9. Technological developments on the Horizon:

a. **Edible Biopharmaceuticals:** Development of oral vaccines by expressing GLP-1 or, insulin renovates treatment paradigms and makes the therapeutic peptides injection independent.
b. **Next-Generation Expression Platforms**: Utilizing Genome modification techniques like CRISPR/CAS-9 mediated genome editing tool, renovating plastid transformation, developing synthetic promoters with tuneable regulatory elements and modular vector systems are ornamental in enhancing precision, yield and competence of plant-based production platforms.
c. **Multigene stacking and combination therapies**: Co expression of multiple proteins that facilitate highly standardized, high throughput production of biopharmaceutical to combat Diabetes.
d. **Automated indoor farming and Bioreactors**: Utilizing Novel protein engineering methods integrating them with vertical farming, hydroponics, controlled environment agriculture (CEA) and plant tissue culture techniques provides a holistic method with high throughput production with minimal environmental variability
e. **Personalized plant biologics**: Convergence of molecular farming with Precision medicine revolutionizes and facilitates of personalized plant derived therapeutics custom-made to individual disease, genotype and microbiome profile.

CONCLUSION

Molecular farming offers a sustainable, accessible, affordable and scalable alternative for global distribution of biologics to the traditional platforms for biopharmaceutical production. In the context of diabetes, a chronic and resource intensive global epidemic, plant based biologics offers a powerful tool to manufacture plant derived insulin, GLP-1 analogs and other therapeutics. The integration of seed-based storage, edible vaccine strategies and glycol-engineering techniques can accelerate the clinical applicability of this platform. However, addressing the implications of this technology, considering the critical biosafety concerns, it is important to cultivate a robust regulatory framework, strategic research investments, public awareness engagement and interdisciplinary collaboration is integral for transitioning Molecular farming a promising concept into an upcoming reality as a mainstream therapeutic solution as a green and globally inclusive approach for diabetes treatment and beyond.

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Author's contribution: Amruta and Ritesh planned the entire study. Amruta wrote the entire manuscript with the support of Riteshkumar. Riteshkumar added valuable suggestions to the study. Both the authors reviewed and approved the manuscript.

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