Review Paper:

Current Perspectives on Plant Molecular Farming: Challenges, Ethical Issues, Regulatory Frameworks, Case Studies and Social Impacts

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Abstract

The production of valuable recombinant proteins using plants as molecular factories is far from classical biotechnology, thus raising ethical, social and regulatory concerns. Molecular farming is a plant-based system exploited to produce pharmaceutical and therapeutic products. This area of plant biotechnology offers a wide span for biopharmaceutical and therapeutic products, but has increasingly been used as a manufacturing industry for a limited range of substances. So far, only a small number of products have made it to the markets, though the number of species expressing merged products, product attributes and the general scale are on the rise. As with the cultivation of traditionally released genetically modified crop plants, issues of justice and 'democratic decision-making' have to be taken into account when releasing molecular farming products.

The imposition of diverse forms of liability for companies conducting field trials of clean phytosimulant crops and the different interpretations that make up 'contamination' were recognized as the engine driving political debates. The current review highlights the challenges, ethical issues, regulatory frameworks, case studies and social impacts of plant molecular farming.

Keywords: Transgenics, expressed proteins, public awareness, intellectual property rights, food security, agricultural community, policy making.

Introduction

The idea that plants can serve as a source of very great diversity in the area of useful or potentially useful compounds has stimulated increasingly high levels of research interest[59]. The products of such research efforts have recently been coined as "natural pharmaceuticals," "green biologics," "renewable resources," "therapeutic proteins," "edible vaccines," and several more metaphoric categories[103].

In this regard, plants generated through molecular biology-based technologies and endowed with genes responsible for the desired products, are envisioned as both low-cost bioreactors and vehicles to deliver these proteins to humans and animals[37]. Currently, in order to actualize this potential of producer systems for a variety of human health needs, the capability of genes has to be translated into feasible, inexpensive and harmless approaches that confer desirable traits.

Several ethical and social issues have also been recognized and were discussed in several workshops, review articles and oral meetings[54]. As long as plants are produced through genetic engineering where there is possibility of the foreign gene to cross species boundaries, is exactly the point of critics' concern[61,62].

Definition and Scope: Plant molecular farming is the production of useful proteins and chemicals by crop and agricultural plants as "bioreactors". This technology represents expression of foreign genes inside an appropriate plant by the techniques of molecular biology, using the wide-ranging biochemical machinery available in cultivable plants[84]. More specifically, in plant molecular farming, useful proteins and non-proteinaceous substances such as oil, biodegradable plastics and remedy chemicals are normally produced either through the exploitation of transgenically altered food crops or through growing non-edible plants[64]. In general, plant molecular farming has two integrated parts. One part includes the traits selected for, of which proteins produced by the plant are a part. The second component acts as a genetic trait to be expressed within the plant cells, thus encoding and guiding the synthesis of "direct" and "essential" proteins.

Upon the biosynthetic proteins being made, newly-constructed molecules get modified according to the plant cellular infrastructure and physiologic environments. Thus, they mostly become fit to execute specific functions or aspects under the target conditions, which have been modulated in the producers[57]. The high market demand for plant-derived active substances, coupled with the growing pipeline of commercialized products, shows that this technology will become a critical technology in producing active substances for biopharmaceutical, vaccination and oral therapeutic products[48]. These advantages make a large-scale production of selected gene products very desirable, for example, recombinant peptides and antibodies in their biological natural system. Nevertheless, plant molecular farming remains a demanding policy to be put into practice due to persistent consideration of environmental problems, the safety of food and ethical (or perceptions of social acceptability) issues.

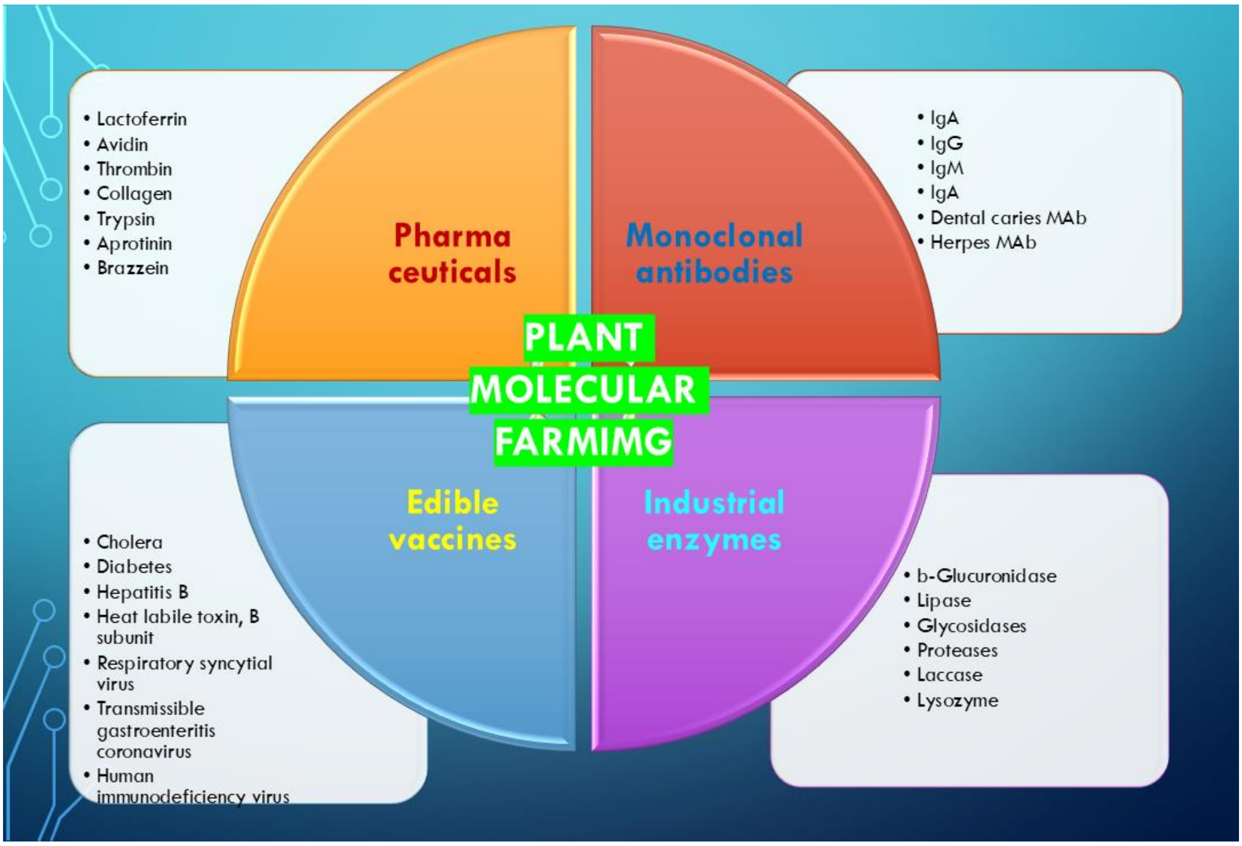

Figure 1: Applications of Plant Molecular Farming

Importance and Applications: Many advantages have been cited for plant molecular farming over the traditional recombinant protein production with microbial or mammalian cells. All the factors required for protein translation and post-translational modification are already present in plant cells[76]. These new plant-based technologies can encapsulate proteins for more efficient topical delivery. Plants may be grown under contained conditions where genetically modified components can be managed[67,96]. In this way, in developing countries, producers of crops from improved seed may be able to extract the protein from the seed of plants grown from these seeds to create vaccines or therapeutic proteins (Figure 1).

In this way, the incentive to adopt improved crops could be considerably increased, especially where larger-scale production of the proteins in facilities cannot be considered[7,73]. As the progress is continuously being made in this ever-growing field, here in this review, we summarize the benefits, prospects and challenges of plant molecular farming. Ethical considerations, regulatory frameworks and case studies are also described.

Overview of Plant Molecular Farming Techniques

Molecular farming involves the production in plants of pharmaceutical, industrial and research proteins. Suppression of intricate body systems in humans can lead to incurable disorders or chronic diseases like cystic fibrosis, diabetes, chronic coagulopathies, inborn errors of metabolism, hormone disorders, nerve atrophy connected with epilepsy, sclerosis or Parkinson's disease etc.[80,83] Human proteins essential raised in plants, needed during the treatment of these diseases, are usually safe, pure, effective and easily accessible. The expression of therapeutic proteins in genetically manipulated plant-based expression systems represents a widely accepted view for their synthesis[10,22].

Plant proteins act as a powerful drug against infectious and chronic diseases and are an innovative source even for diagnostic applications. The green fluorescent protein and the human protein placental-like alkaline phosphatase easily aggregate in the plant cells[19,72,95].

Genetic Engineering Methods: Genetic engineering is the set of techniques used in the handling of cells' genetic material. This technology involves splicing DNA from any organism in some form. Molecular farming aims at producing a new cellular or developmental process[82,98]. Plant molecular farming offers benefits in large-scale production at a relatively low cost of production, enhanced safety and correct folding and glycosylation of the recombinant proteins produced in plants[25]. The relatively easy genetic manipulation of plant expression systems in relation to transgene design, reproducible transgene expression, post-translational processing and accumulation of properly oriented foreign gene, results in production of biologically active proteins[15,68]. Several genetically engineered plants are already available and more are being constantly developed. Some of these data can be taken in food such as tomatoes,

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corn and soybeans[43]. In the process of recombinant DNA, some of the characteristics are played by restriction enzymes. This type of enzyme naturally occurs in bacteria and other types of prokaryotes, which cut DNA, not part of their own chromosomes. It would make sense that a restriction enzyme would recognize DNA sequences in chromosomes from different organisms. For example, human DNA could be "cut" or altered to accept a new gene of bacterial origin that would not have been part of the original human genome.

For instance, the new gene is combined with DNA vectors, a plasmid is recombined and its DNA starts to replicate itself in an independent fashion from a large chromosome using bacteria[26].

Many plants with sets of genes that are identical, are known as clones. This process enables the gene to be "moved" to a desired place in the process of DNA cloning by harnessing mechanisms that organisms use in their natural repair of broken chromosomes. One of the key results in molecular farm production is giving genes to plants which end up encoding proteins that the plants are not naturally capable of making[85,94].

Plant Transformation Techniques: Plant transformation techniques allow for the introduction of foreign genes in plants: gene transfer mediated by a (1) natural pathogen of plants, *Agrobacterium tumefaciens*-mediated plant gene transfer, or co-cultivation of plant cells with this bacterium, (2) DNA coated onto accelerated particles through the plant cell wall, (3) transfer of linked genes through engineered pollination by microinjection or isolation of the zygote and many more. Plants with new foreign genes are regenerated and self-pollinated until plants bear the new linked marker genes on F1 seeds selected at desired plants having the new foreign genes. The above-mentioned plant transformation techniques used in generating transgenic plants need to have precautions taken into consideration with suitable molecular makers[6,33,66,106].

Benefits and Challenges of Plant Molecular Farming

In 1986, Arntzen conceived a genetically modified plant cell-based system producing pharmaceutical agents, now more commonly called "molecular farming." The discovery broadened the applications of biotechnology from only food, feed and fiber to pharmaceutical, nutraceutical and industrial products (Figure 2)[90].

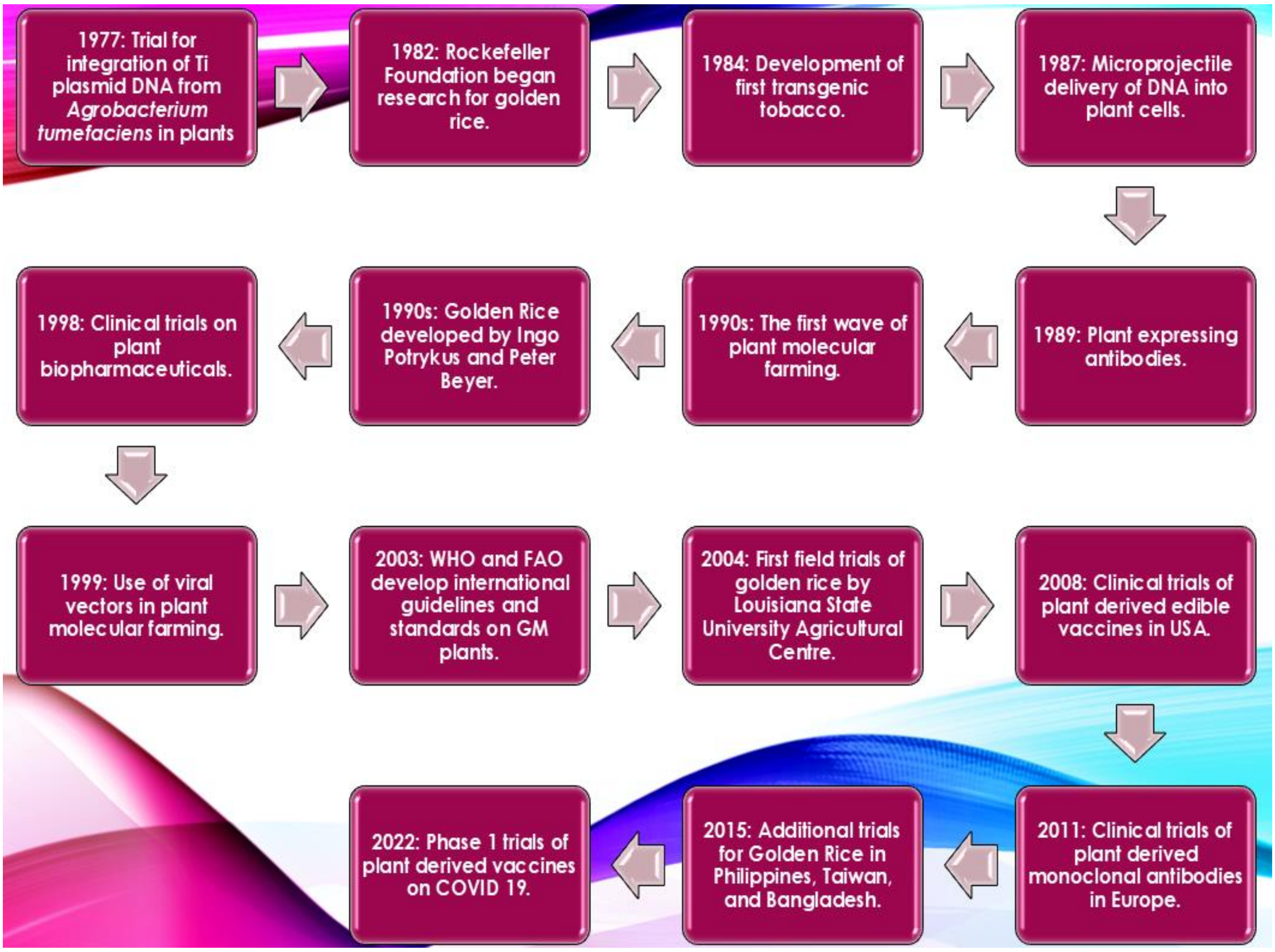

Figure 2: Major historical developments in Plant Molecular Farming

Advantages of Plant Molecular Farming: The US economy has been very volatile over the past two decade. In doing so, it has shown one of its characteristics of being a capitalistic economy: it expands and contracts. Throughout this financial market, demands on society have been placed upon new and innovative products and new jobs[99]. It is through this backdrop that plant molecular farming enters the playing field. The maturing of the biotech industry is primarily responsible for this predicted economic explosion. The biotech industry as a whole is quite optimistic about plant molecular farming. It is expected that plant molecular farming will register exponential growth and will continue to remain at the top in terms of number of patents compared with other biotech industries[45].

Indeed, the most commonly associated benefits of plants in pharmaceutical production include low production costs, high yields, scalable and flexible production platforms, versatile processes, some of which do allow for the development of products that would otherwise never reach the market. Technical challenges are still to be overcome including the development and approval of an effective plant expression platform for many recombinant molecules, polypeptides and antibodies; technical competitiveness, compliant with good manufacturing procedures although not necessarily pharmaceutical grade and cost-effectiveness for the target markets, including specific industrial uses and important therapeutic applications[58,63].

Public Awareness Challenges: Plant molecular farming used to be touted as the magic bullet solution to many of the world's problems, but it has also been implicated in various ethical and safety issues that have not yet been resolved[91]. Plant molecular farming for the production of pharmaceuticals in food crops is one such application among many genetic manipulations made on flowering plant species to produce a plethora of mostly small value or low volume, high value, high-technology compounds: vaccines, human or animal antibodies, pro-drugs etc. Food-borne vegetables and fruits, grains, tobaccos etc. are being used to express such products.

Public awareness about plant molecular farming is necessary to provide proof of ethical admissibility, to open the possibility for controlling regulatory procedures and their results including active support of the use of technology by different actors and stakeholders. It must, above all, leave behind a residue of public trust in the technology and in the political management of emerging biotechnological applications[34,100].

Ethical Considerations in Plant Molecular Farming

Plants are rich in many vital molecules including proteins, but isolating higher quantities from them is cumbersome. Many such molecules can now be produced in a genetically modified plant, such as tobacco, at a fraction of the cost of their production from natural sources at present. However, plant molecular farming has raised some moral questions. The perceived threat becomes imminent as the pool of transgenic crop plants reaches the marketplace and with the risks high, ethical, moral, philosophical and social questions multiply, as also do risk management problems. High-stakes policy decisions will crop up on similar considerations as the one which arose in the area of recombinant DNA research[13,93].

Intellectual Property Rights: It is a very complex activity in plant molecular farming and gives rise to unique problems while raising specific issues in ethical and legal questions. The variety of the seeds has been patented, which means they cannot be used to produce food. While that is an absurdity of society, it is much like a potential one: multinational corporations are possessing the most varied and richest plant genetic heritage while preventing populations that possibly contributed to the development and multiplication of those very same seeds from using them[4,38]. Another key issue with plant molecular farming is that it has a bearing on farmers' sovereignty and rights. This tendency would generally slide in an implicit way towards global control of food and the agricultural production system as a whole[16,71].

The concentration in the sector of ownership of technologies and access to genetic heritage is such that farmers increasingly feel deprived of acquired rights to use seeds freely, reproduce, maintain and sell traditional seed varieties. This is, therefore, an enormous ethical problem, threatening both the survival of traditional agricultural practices based on techniques of integrated production and the well-being of millions of small farmers in underdeveloped countries who do not even have access to seeds. Of course, one of the most problematic aspects concerning the ethical sustainability of plant molecular farming is resorting to artificial needs in order to force the selling of new products[17,78].

Access to Technology and Resources: Technologies and related resources that are required for the biotechnological production of plant-made pharmaceuticals and other high-value compounds are expensive and distributed unequally between the developing and developed countries. Therefore, it has been of major concern to see the application of modern biotechnology in promoting economic development and in achieving food security for millions of poor people around the world. It has thus forced the international community to work out the conditions and mechanisms under which effective and efficient technology transfer and capacity strengthening can be realized in the process of implementing international agreements such as the Convention on Biological Diversity, World Trade Organization and Food and Agriculture Organization[24,28].

The countries not endowed with the latest knowledge and technologies regarding the pre-treatment of plant cells, gene transfer, selection of transgenic plants and gene containment are net users of the technology. Principles of participatory technology development, intellectual property rights, biosafety, benefit sharing and capacity building and creation of an enabling environment both at the national and international levels, need to be complied with[81]. The same technology and resources used to meet the needs of the developed and developing countries that have to respond to worldwide requirements for food, feed and nature-like, face the population explosion and mounting demand for non-food products besides medicines, vaccines and diagnostics. The technology transfer should include the denominator of the commercial size of the plant-incorporated product. Therefore, faced by such diversification and demand from many users, the technology transfer should include denominators of the commercial size of the plant[14,50,86].

Regulatory Frameworks and Guidelines

Guidelines development in plant molecular farming is very critical because it gives an assurance of safety and consistency of the end product. Moreover, following the data and standards presented, will ensure a guarantee of sustained development of the biosafety framework. Therefore, the regulatory authorities for the commercial release of plant-derived pharmaceuticals have particular policies in place to regulate their safety and efficacy for the development of human and animal health. Its application extends to the combination of the regular flow of the pollinating pollen, it may require greater attention, particularly in the development of policies for gene flow and the coexistence of genetically modified and non-modified crops. Environmental risk analysis in plants with a pharmaceutical-contained system may be used as a model for the implementation of the new guidelines[11,35,36].

International Regulations: The promising tool offered by plant molecular farming implies a wide array of regulations. The United Nations General Assembly, able to take decisions only on critical issues, approved an optional "Biosafety Protocol" in January 2000, concerning the International Convention of Biodiversity[2]. This text was sent to the Economic and Social Council and to the Trusteeship Council for adoption, with a view to obtain the largest possible number of parties able to approve it and to ratify it.

Already, several countries have signed and ratified it, but a number of countries are still opposed to these regulations[5]. In some countries, this set of regulations is already enforced and subsequently controlled. The European Community also incorporated the Biosafety Protocol into a regulation within two years since its sentence was issued (Table 1)[23].

Worldwide Legislation and Oversight: The use of plants as bioreactors can be immense, but it will equally call for public consumer acceptance and periodic scrutiny comprising standards in documentation, procedures for inspection and status monitoring. Indeed, many countries and regions, such as Europe and North America, have legislated on plant molecular farming and regulations on cultivation of plants with respect to the effect on the environment in the course of the field trials[87,105]. This difference in regulation is often country-specific.

As an example, while members of the European Union have different regards for transgenic crops as part of the national laws, under one standard EU law, they all are regarding cross-border trade for growing, importing and deploying genetically modified crops[18,55].

Under current global circumstances, the vast majority of events of genetically modified crops in open environments are intended for use in medical and pharmaceutical services that would have a net positive effect on human health and welfare.

Social and Economic Impacts of Plant Molecular Farming

Food Security and Access: The rapid social changes associated with the industrial revolution and the resulting urbanization were very destabilizing, leading to years of serious social upheaval. Now, similar changes in society are occurring in developing countries moving from largely rural, agriculturally-based economies to urban, industrially-based economies. There is no question that these changes are also very destabilizing for people associated with agriculture. This is particularly so for small-scale farmers who depend on subsistence farming to meet their daily needs[9,30].

It is of great concern therefore that the bulk of the 800 million under-nourished people in the world are found in the rural areas of developing countries and depend mainly on local agriculture for subsistence. Such communities would require a fine balance at the local level between adequate production of food for subsistence and maintenance of vigor in the local environment[1]. It is not adequate that people in developing countries should be able to feed themselves at a subsistence level; they should always be able to produce a surplus of food that can be sold to provide the cash necessary to access the educational and medical facilities that will bring substantial improvements in their standard of living[53,60].

Economic Development: The economic benefits that are expected out of plant molecular farming will be huge, with the ability to maximize agro-industrial efficiency. New wealth can thus be created with this venture by rejuvenating agriculture with a high-tech industry. It will benefit the communities that have been economically devastated by the shrinking returns from industrial farming, particularly small-farm owners and operators in developing economies, who can now participate in this high-technology market without large capital investments in research and development, specialized facility construction and management and huge chemical feedstock inventories. Sounder and more productive agriculture will derive from rural economic revitalization from local facility construction and operation and from local crop sources[21,39,56].

Table 1
Various Regulatory Frameworks Organizations for genetically modified plants across the globe

S.N.	Regulatory Frameworks Organizations	Location
1	Australia New Zealand Therapeutic Products Authority	Australia
2	Brazilian Health Regulatory Agency	Brazil
3	Canadian Food Inspection Agency	Canada
4	Committee for Medicinal Products for Human Use	EU
5	Committee for Risk Assessment	EU
6	Committee for Socio-economic Analysis	EU
7	Directorate General Health and Food Safety	European Commission
8	Department of Biotechnology	India
9	European Chemicals Agency	EU
10	European Food Safety Authority	EU
11	European Medicines Agency	EU
12	Food and Agriculture Organization	UN
13	Food and Drug Administration	USA
14	Genetic Engineering Appraisal Committee	India
15	Health Canada and Environment and Climate Change Canada	Canada
16	Health Canada's Biologic and Radiopharmaceutical Drugs Directorate	Canada
17	Health Canada's Health Products and Food Branch	Canada
18	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	Switzerland
19	International Service for the Acquisition of Agri-biotech Applications	Philippines
20	Ministry of Environment, Forests and Climate Change	India
21	Organisation for Economic Co-operation and Development	Paris
22	Registration, Evaluation, Authorisation and Restriction of Chemicals	EU
23	Review Committee of Genetic Manipulation	India
24	Scientific Committee on Consumer Safety	European Commission
25	Scientific Committee on Emerging and Newly Identified Health Risks	European Commission
26	Scientific Committee on Health and Environmental Risks	European Commission
27	Southern Agricultural Council	South America
28	U.S. Code of Federal Regulations	USA
29	United States Department of Agriculture	USA
30	US National Institute of Health	USA
31	WHO Codex Alimentarius Commission	Italy

Case Studies of Plant Molecular Farming Projects

Golden Rice Project: The Swiss Federal Institute of Technology launched the Golden Rice project together with the American organization Rockefeller Foundation and the Washington University. It involves the insertion of two carotene biosynthetic pathways into rice, which nowadays is cultivated worldwide on a big scale[79]. One pathway uses the daffodil codifying gene, while another comes from the bacterium *Erwinia uredovora*. Both pathways are co-expressed in the endosperm and the result is an orange seed color. Estimates show that two hundred grams of the transgenic rice are able to supply 50% of the daily required vitamin A for a human. When the first attempt to create golden rice with genes taken from daffodils was done, little shoots began growing around the seeds in the culture dish. The daffodil genes had copied themselves into the bacteria, which moved into the rice from the bacteria in their lab.

With this evidence of plant escape of the transgene, one can understand that opponents of GM techniques are concerned that some of the synthesized beta-carotene could be released into the soil by decomposing rice plants, potentially moving into wild relatives of the rice or other species and potentially disrupting healthy ecosystems. Although the beta carotene of the seed does not seem to limit insect infestations, there are both health and ecological concerns relating to the potential contamination of the environment with non-engineered or transgenic plants that were created to be insect-repellant either by the way of acting as insect bait or through the spreading of pesticide genes to the bacteria of the soil. Another area of ecological concern arises with respect to the unpredicted interaction of the dietary condition promoted by biopharming with naturally occurring or synthetic toxic elements of the environment[3,42,65].

Vaccines produced in Plants: There are various reasons for producing recombinant subunit vaccines in plants, but some of these same reasons also present ethical concerns for plant molecular farming. Recombinant subunit vaccines produced in plants are safe because of the absence of infectious materials. There is, therefore, no need for viruses produced in plants that form part of any GM crops designed to protect against viral infection in the production of vaccines[69,74]. Plant molecular farming allows for the relatively easy production of relevant antigens in large quantities in developing countries or remote areas, easing worldwide vaccine distribution. Plant molecular farming is also able to produce animal health vaccines, which are required to produce safe food, including recombinant subunit vaccines against the zoonotic diseases not present in all of the trading partners, for example, Japanese encephalitis, Rift Valley fever, or avian influenza-icterohemorrhagica diseases[88,103].

Because an antigen will be produced by a GM crop with an antigen-producing gene in its DNA as opposed to by a microorganism, recombinant subunit vaccines produced in plants are perceived as having less potential for contaminating the environment or posing any food safety concerns. However, some plant molecular farming systems will impact negatively on the environment and food consumption, thereby human health. This is particularly true for seed-produced antigens or if the antigens are soluble and hence likely to be released for uptake by pollinators[29,40].

Engagement and Communication Strategies

Public engagement is of paramount interest to the stakeholders of plant-made pharmaceuticals and might have an important role in building trust and acceptance of plant-derived pharmaceuticals. Value judgments about the potential effects of plant-made pharmaceuticals research are explicitly recognized in funders' and institutions' policies related to the performance of this work[97]. Legislation on release of genetically modified plants to the environment should be debated in society. Special efforts, however, must be made to avoid any kind of discrimination or non-transparent debate. The setting of the framework for responsible science, public-private partnership and public participation in all areas concerning plant molecular farming research and development must be made[20,41]. Molecular farming of agriculture crops should consist of open and broadly inclusive dialogue among a large number of stakeholders from both the public and the private sectors[31].

Stakeholder Engagement: In particular, plant molecular farming is a global multi-stakeholder business enterprise that links challenging and controversial areas of modern plant molecular technologies and agriculture with GM plants. While normally modest efforts have been made to convene expert meetings to discuss and develop governance models which might guide scientific and industrial practitioners in the plant molecular farming field. An initiative of the International Society for Plant Molecular Farming provided a platform and opportunity to address at least this general deficit in stakeholder engagement[77]. There is a need to identify much of the wide-ranging scope of ethical issues implicated in plant molecular farming, including the multinational legal and regulatory gaps across a myriad of issues like biosafety, biosecurity and risk and corporate social responsibility to preclude the dangerous re-surging form of global neocolonialization[46].

Public Perception and Awareness: Public perception about new technologies is highly dependent upon awareness levels and the resulting information given to the public. Plant molecular farming due to genetic engineering has resulted in the development of pharmaceuticals and complex proteins[51].

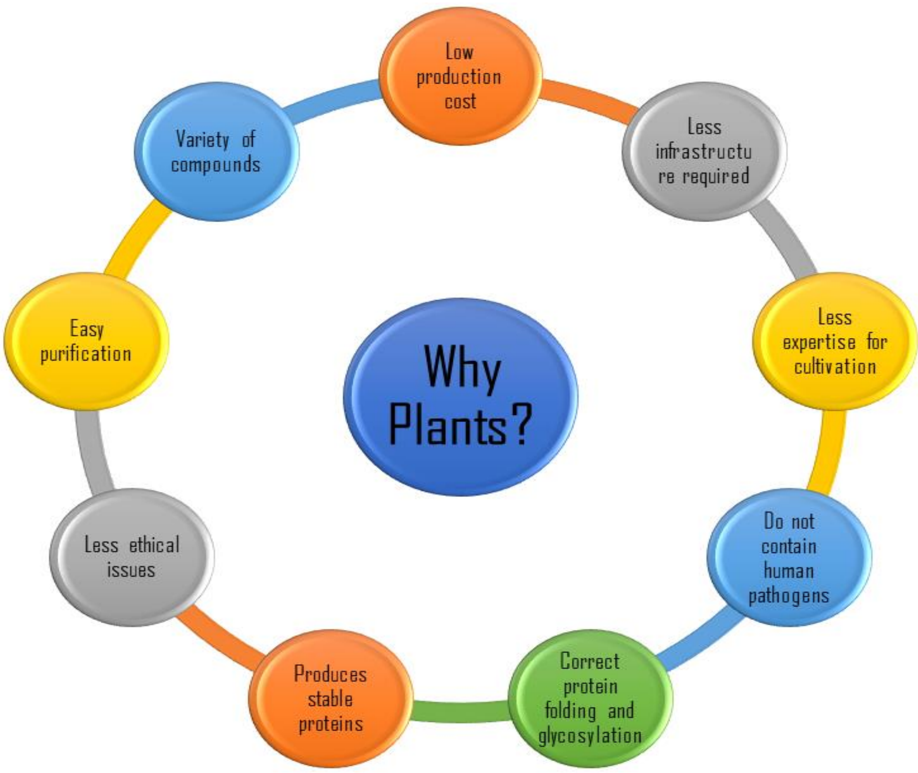

Figure 3: Reasons why plants are considered best for Molecular Farming

Since it is a process related to food crops, ethical issues of food safety and right to access to medication and nutritional value arise. With economic factors and genetic advantages, the agricultural sector becomes a valuable candidate in the supply of pharmaceuticals on demand[70,89]. Knowledge of considerations for the ongoing market and modeled plants will provide benefit to producers and consumers, giving information for increased acceptance of such products (Figure 3). For example, in the case of plant-derived vaccines, requirements about vaccine safety, food safety, efficacy and informed consent were identified as those requiring ethical clearance based on these principles.

This informed consent required patient awareness of genetic vs. non-genetic vaccines, multinational collaboration for its approximation, safety and tracking of the vaccine from the bioreactor to the plant and human host, neural tube defects publishing, intrusive vs. non-intrusive vaccines, advantages of plant-derived vs. bioreactor-generated vaccines and determination of the infectious status of vaccines[49,92,102].

Future Directions and Emerging Technologies

In plant molecular farming, as with almost every technology, public debate and discourse run in parallel with the development and commercialization. Although such a velocity in development and commercialization may already be a cause of alarm for many, given that significant questions and concerns have only been partially or totally left unanswered or unaddressed. If concrete actions are not taken to address these concerns, public focus on the promise of plant molecular farming could soon be overshadowed by its potential drawbacks[12].

Trends in Plant Molecular Farming Research: With the advancing biotechnology, an increasing array of transgenic crops are being used to manufacture complex protein pharmaceuticals or enzymes. There is immense interest among biotech and pharmaceutical industries and also among academic research institutes in the development of new production systems that turn out such materials more efficiently and more cheaply than traditional microbial fermentation or animal cell culture systems. Industries also wish to minimize the complexity in production and consequently the risk of contamination by endotoxins or other unwanted products. Such alternatives to the conventional fermentation systems for proteins should, therefore, appreciably enhance the commercializing potential of such costly proteins and eventually make them more widely available as drugs or for biotechnological applications.

The new expression systems also arouse growing interest for fundamental scientific and applied research[8,32]. Such traits in these bio-pharm crops raise concerns among critics about unintended effects on the environment, particularly gene flow into related wild species or sexually compatible weeds that could be dramatically affected by such traits in terms of fitness and survival. There is also a fear that unwanted proteins may enter the human food chain through genetic contamination, which, although statistically extremely low, as death from bioengineered crops is, could have disastrous consequences if the protein was toxic or immunoactive, especially in populations with a predisposition of susceptibility to the expressed protein[27].

Commercial-scale production has focused on biopharmaceuticals from transgenic farm animals and fermentation systems, with only one biopharm crop getting limited FDA approval as Du Pont's Project BioShield work on anthrax vaccine. These are plants grown for reasons such as phased, or conduct clinical trials and have come to be a small fraction of the total value of plant biotechnology[75].

Potential Ethical Issues in Future Technologies: Advances in scientific knowledge and technology hold out the prospect of mitigating many of the ills which afflict human society, from disease and disability to malnutrition. Just at the time when the potential of biotechnology to deliver such benefits is increasing, however, there is popular opposition to its use in agriculture, food production and medicine. But does this mean that biotechnology researchers and the bio-industry have a 'social license' to proceed with research and development?[52,101] The mixture of science and technology concerns and the activity of scientists, technologists and industry, stemming from a complex mixture of differing values is often not well expressed. Disagreement and ignorance are reinforced by the risk of real or perceived disasters ensuing from the application of complex and novel technologies.

There are more serious concerns associated with the release of novel genes and gene products into the environment or into the food chain[44,47]. The introduction of value-laden genes into staple food plants and crops themselves raises concerns, as 'the untended gene'. Increasingly valuable primary medical products are removed from normal commercial trade. These are some of the reasons that justify increasing concerns about plant molecular farming. While many of these concerns have been aired, their validity has not been intensively examined and tested, especially with the stakeholders and the general public who have or might have investments in these commercialized genetically modified plants and have the power and influence to raise or reject what is progressively described as further 'social licenses' for the technologies.

Conclusion

Plant molecular farming technology will have broad-based proletarian applications, particularly for the self-employed agricultural sector of developing countries. Indeed, it is estimated that increasing adjuvant costs alone would raise protein production prices twentyfold and at present, molecular farming products will raise the prices. By providing an outlet for excess agricultural production through the infrastructure of conventional crops, plant-modified protein will stimulate farm commodity and cash crops pricing as a by-product of conventional crop harvest and hence shall have a positive effect on the general agricultural community.

The main issues in plant molecular farming fit into the ethical, legal and social frameworks surrounding more widely established biotechnological practices. Even so, the unfamiliar transfer of established techniques to a new culturing system, the occasional need for new methods to ensure their use is seen to be safe and ethical motivations that inspired its development, have their associated ethical challenges.

Although these challenges appear to fall within the framework of what has already been established in biotechnological practices, they may require further refinement and specific attention with respect to these new practices. With genetically modified plants, the ethical arguments seem to translate into a two-dimensional appraisal of safety and justice.

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