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Contemporary Advances and Precincts of Biopharming as Drugs' Production Systems

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Abstract
The pharmaceutical industry has been criticized for not availing more innovative medicines for treatment of emerging and changing diseases. The sharp decline in the number of new drug approvals in the last decade can be attributed particularly to attrition of the small organic molecules during origination and development. Constraints to traditional drug discovery are compounded by among others drug candidates for central nervous system (CNS) disorders facing additional barriers than those intended for other therapeutic application. Additionally, the antineoplastic agents precipitate severe toxic effects. Currently, the prohibitive cost of biopharmaceuticals limits their availability and use. It is therefore becoming imperative that alternative approaches, like biopharming, be considered as avenues for availing medicines for such illnesses. Moreover, increasingly, attention is also shifting to larger and more complex protein molecules as therapeutic agents. Through an extensive review of published literature on recent studies, this paper presents fundamental intuitions that continue to be recognized as advances and precincts. The solution seems to be in more use of biotechnologically plant-derived biopharmaceuticals and humanized substances. The contemporary biopharmaceutical production systems involves transfecting cells using bacteria and virus or by biolistic delivery method; exploration of Genetically Modified Drugs (GMD); and Plant Made Pharmaceuticals (PMP). All these have presented advantages like low costs and an already available technology for harnessing. However, uncertainties range from competing platforms, unresolved technical problems, patent and regulatory issues, potential risks to human health, issues of gene spread, and animal-welfare concerns. Cultivating plants to manufacture drugs would involve many controls and regulations that differ from region to region across the globe in respect to the regulatory authorities. Meanwhile African perspectives on genetically modified organisms need to focus on the science and learning for formulation of policies and agreements to harmonize national and regional bio-safety policies. In conclusion, Pharmacists need to appreciate the huge responsibility that comes with biopharming and, especially, the need for stringent professional, ethical and regulatory controls.
Keywords: Biologics, Biopharmaceuticals, Biopharming, Genetically Modified Drugs, Plant Made Pharmaceuticals

1. INTRODUCTION

Until recently, medicines have been largely small organic molecules produced through chemical or microbial syntheses. These include most antibiotics, analgesics, hormones, and other pharmaceuticals produced in the pharmaceutical industry. Currently the pharmaceutical industries are being criticized for not availing more innovative medicine to the market for treatment of emerging and changing illness (Gagne & Choudhry, 2011). This is as a result of the current innovation deficit in pharmaceutical research and development (R&D). The sharp decline in the number of new drug approvals in the last decade can be attributed particularly to attrition of the small organic molecules during discovery and development. The success rate from phase-III clinical trials to market translation is reported to be 50–70%. The small molecules are dropped during preclinical stage and withdrawn from further development during clinical studies for various reasons, such as lack of efficacy, toxicity, poor absorption, distribution, metabolism and elimination (ADME) properties, commercial interest and market competition (Prentis et al, 2012). However, the failure of drug candidates may not be limited to the aforementioned (Basavaraj & Betageri, 2014).

There have been several approaches suggested to reduce attrition of drug candidates in clinical development including identification of right target and strong mechanism of action, and the identification of biomarkers. It is therefore becoming imperative that alternative approaches, like biopharming, be considered as avenues for availing medicines for emerging illnesses. Moreover, increasingly, attention is also shifting to larger and more complex protein molecules as therapeutic agents. While bacteria make convenient production systems for these protein molecules, they are incapable of most of the post-translational modifications necessary for the activity towards fruition of many mammalian proteins. This has called for consideration of higher organisms with more advanced systems for this purpose (Ahmad, 2014). Other production systems, including microbial eukaryotes (yeasts, double-stranded fungi), animal cells, and transgenic animals, have therefore been tried but later replaced by transgenic plants as a result of their limitations. Plants are advantaged in this regard for several reasons: first, they have a higher eukaryote protein synthetic pathway, like animal cells, with differences in post-translational modifications (e.g. glycosylation) in proteins which, although minor, could make a recombinant protein inactive,

harmful or immunogenic. On the other hand, bacteria cannot produce full size antibodies nor perform most of the key mammalian post-translational modifications. Secondly, proteins produced in plants accumulate to high levels and plant-derived antibodies are functionally equivalent to those produced by hybridomas. Thirdly, plant expressed proteins are not contaminated with human or animal pathogens (HIV, hepatitis viruses) nor are they co-purified with blood-borne pathogens or oncogenic sequences (Ahmad, 2014).

Researchers have used Genetic Modification (GM) to increase the yield of plant products by given traits, including the responses of herbs to abiotic and biotic stresses. The use of Genetically Modified Organisms (GMO's) has permeated agriculture, medicine, research and environment, with both positive and negative effects (Gavanji, 2013). In 2010, for example, biologics accounted for more than 50% of all new drug approvals (Tschofen et al., 2016), a revolution mostly due to the rapid explorations and research into plant-based expression of pharmaceutical proteins (Rosin, 2004; Tschofen et al., 2016). Selective breeding has been existing since the Darwinian era (giving rise to grasses like wheat, rice and maize). Before the introduction of hybridization and selective breeding, wild rice and maize produced fewer seeds, providing a smaller amount of food for human consumption (Ahmad, 2014). Creation of GMO's involves the biotechnological engineering of organisms in the laboratory purposely to favor specific environmental trait(s). This manipulation of molecular and structural nature of DNA and RNA can cause major changes in function and expression of other macromolecules.

As one of the several recent biotechnology applications that go beyond the traditional agricultural products of feed and fiber, biopharming entails the production of pharmaceutical proteins in genetically modified (GM) plants, animals and micro-organisms (Gagne & Choudhry, 2011; Kermani, 2006). When plants only are involved, it is known as plant-based pharmaceuticals (PBP). In this technology, genes that code for useful proteins are inserted into plants or animals which then produce the pharmaceutical product in large quantity. These biopharmaceuticals are cheap to produce and store, easy to scale up for mass production, and safer than those derived from animals or microbes. The widely explored categories can be grouped as: parenteral therapeutics and pharmaceutical intermediates, industrial proteins, monoclonal antibodies, and antigens for edible vaccines. This paper is intended to review in some depth the traditional drug discovery challenges; and biopharming application techniques, regulations, and products relevance as therapeutic agents. Suggestions are also made of novel strategies for researchers and pharmaceutical industry to provide products and solutions for emerging illnesses.

2. METHODOLOGY

Literature search was carried out using respective search engines including Google Scholar, PubMed and HINARI with search words as 'Biopharming'; 'Drug Discovery'; 'Pharmaceutical Biotechnology'; 'Pharmaceutical Microbiology'; 'Industrial Pharmacy' and 'Molecular Pharmacy'.

The accessed published works, including peer reviewed journals, working reports and policy documents in the area of interest, were screened out for review based on period of publication that stretched for the period 2010 to 2017. These were then followed by a compilation of the Contemporary Advances and Precincts of Biopharming as Drugs Origination under the following topics.

3.0 BIOPHARMING TECHNIQUES

3.1 Constraints of Traditional Drug Discovery

It is reported that only 15% of molecules entering the clinical trials receive marketing approval (Kwong et al., 2011). The success rate from phase-III clinical trials to market translation is reported to be 50 - 70%. The molecules are dropped during preclinical stage and withdrawn from further development during clinical studies for various reasons, such as lack of efficacy, toxicity, poor absorption, distribution, metabolism and elimination properties, commercial interests and market competition (Prentis et al, 2012). The failure of drug candidates by traditional strategies of drug discovery may not be limited to only the above listed, there are several challenges that have turned out to be constraints to the entire process of coming up with novel drugs. The challenges vary greatly, depending on the particular method, and include the following:

- Drug discovery and development of drug candidates for central nervous system (CNS) disorders face additional barriers than those intended for other therapeutic application. While the CNS drugs exerting activity may lead to unwanted changes in the brain physiology and neurochemical balance, the blood brain barrier (BBB) also poses another barrier for development. Drug candidates envisioned for CNS application thus require stringent safety requirements.
- There have been significant innovative solutions to address such issues like absorption by enhancing solubility and permeability of molecules. However issues such as rapid metabolism, especially first pass effects, still remain serious challenges with very minimal progress. Resveratrol (RSV), a natural biochemical with diverse biological activity, has limited clinical application due to its rapid metabolism in the body leading to absorption of only its metabolites after oral administration. This is due to

complete pre-systemic metabolism (Basavaraj & Betageri, 2014).

- Then there is the case of antineoplastic agents which tend to be toxic chemicals and biologics designed to kill the cancer cells. Their drawback is that while exerting desired pharmacological effects, they precipitate severe toxic effects (Schweitzer, 2015).

Most of the reports however focus more on solubility and permeability issues for the small molecules to be applied as drugs. This hence illustrates the dire need of alternative formulation strategies like biopharming to be embraced in explorative drug discovery and development.

3.2 Biopharming Techniques & Products Relevance

The use of plants for medicinal purposes dates back thousands of years but genetic engineering of plants to produce desired biopharmaceuticals is a much newer phenomenon propagated by the technological advances of the 21st Century. As the demand for biopharmaceuticals increases, it behooves us to ensure that they are available in significant quantities but cost-effectively. Currently, the prohibitive cost of biopharmaceuticals limits their availability and use. The solution seems to be in more use of plant-derived biopharmaceuticals which are cheap to produce and store, easy to scale up for mass production, and safer than those derived from animals. Most antibodies expressed to date have been in tobacco. Tobacco produces large quantities of green leaf material per acre, with a highly efficient agrobacterium-mediated transformation. Its seed production is prolific, which could facilitate biomass scale-up; the plants mainly self-pollinate, so there is little risk of transfer of genetic material to other plants; and, as a non-food crop, there is little risk of food chain contamination. Unfortunately, tobacco has high quantities of unwanted secondary metabolites like nicotine in its leaves that could make the expressed proteins less usable. However, there are tobacco cultivars able to produce reduced levels of these metabolites (Ahmad, 2014). Alternatively, efficient purification could be done to get nicotine-free recombinant proteins (Goven et al., 2008). Other leafy crops that have been used for recombinant protein production include spinach, lettuce and lucerne (Ahmad, 2014), although more recently carrots, algae, moss, potatoes, soybean, alfalfa, rice and wheat have also been used successfully (Kwong et al., 2011). Proteins may be unstable in the leaf environment, interfering with yield and quality of the protein. Also the phenolic compounds released during an extraction process could be detrimental to downstream processing. Seeds on the other hand have specialized storage compartments which help in reducing protein degradation and avoiding exposure to phenolic compounds, thus improving downstream processing (Ahmad, 2014).

Spirulina (*Arthrospira platensis* and *Arthrospira maxima*) is a cyanobacterium, and nature's richest super nutrient with low cost of production compared to plants. It has both prokaryotic and eukaryotic characteristics, making it excellent for biotechnological applications. Spirulina has been exploited as a photosynthesizing bioreactor for efficient production of a wide variety of biotechnology products. It has clear advantages over other plant nutrients. First, its protein content makes up to 70% of its dry weight, thus could store high doses of edible vaccines. Secondly, spirulina biomass includes all essential amino acids; large amounts of health promoting lipids; essential (omega) fatty acids, ω-3 and ω-6 polyunsaturated fatty acids; a huge collection of vitamins; a great deal of potassium and various minerals. Finally, spirulina has ten mixed carotenoids, with its β carotene being ten times more concentrated than that of carrot (Kermani, 2006).

3.3 Biopharming concepts

Biologics are drugs that are made in living cells and include recombinant proteins, vaccines, and monoclonal antibodies. Biopharmaceuticals are medicines produced through biotechnology by means other than direct extraction from a native (non-engineered) biological source. They are typically manufactured through fermentation processes involving bacteria, yeasts, fungi or algae, or through cell cultures from insect, plant or animal cell systems (Breyer et al., 2009). Animal biopharming is defined as the farming of transgenic animals genetically modified to produce "humanized" pharmaceutical substances for use in humans (Breyer et al., 2009). Plant-made pharmaceuticals (PMPs) are therapeutic proteins, antibodies, and vaccines made in genetically-modified plants. This practice of using plants to produce human therapeutic proteins is variably called pharming, biopharming, and plant molecular farming, PMF (Kwong et al., 2011; Aldridge, 2013; Mohanty & Kumar, 2013). Biopharming is thus one method, or "production platform", for the production of biopharmaceuticals (Mohanty & Kumar, 2013). It 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 (Ahmad, 2014). Biomolecular engineering is the application of engineering principles and practices to the purposeful manipulation of molecules of biological origin. Biomolecular engineers integrate knowledge of biological processes with the core knowledge of chemical engineering in order to focus on molecular level solutions to issues and problems in the life sciences related to the environment, agriculture, energy, industry, food production, biotechnology and medicine (Anon., 1987). Genetic modification of plants involves transferring a gene for the protein drug to a virus or bacterial vector that will take the gene into plant cells. Then these cells are cultivated under carefully controlled conditions, using well studied and characterized plants allowing for effective risk assessment and

tracking of the transgene of interest. The seeds or leaves of these plants are harvested to obtain the drug (Ahmad, 2014). Promoter is a segment of DNA occurring close to the coding region of a gene and acting as a controller over when and where the gene is expressed.

3.4 Contemporary Biopharmaceutical Production Systems

There are many methods of transfecting cells (DNA-mediated gene transfer, microinjection, electroporation, polyethylene glycol (PEG)-mediated protoplast fusion, lipofection and viral transfection) and for many cell types, gene transfer using these methods has become a routine tool for studying gene regulation and function (Abiri et al., 2015; Fitzgerald, 2003). Although most of these systems are robust, scalable and cost-efficient platforms, two key methods for gene introduction have evolved that yields a PMP into a host plant (Pablo, 2010). The first involves using a bacterium or virus that naturally infects the plant as a vector, like the bacterium *Agrobacterium tumifaciens* (in agrobacterium-mediated transformation of dicotyledonous plants). The second is called "Biolistic" (gene gun) delivery method, used in monocots (Ahmad, 2014). In the latter method, devised and used by Theodore M. Klein and John C. Sanford, a gun is used to fire metallic microprojectiles (1.6 µm gold or tungsten) coated with DNA and RNA directly into plant cells. The nucleic acids are "transiently expressed", that is, they produce protein in the plant cells. These cells are not harmed by the high speed bombardment (Abiri et al., 2015) and those that have taken up the gene are generally identified by the presence of an antibiotic resistance marker gene, transferred alongside the gene. Electroporation is a silicon carbide fibre-based technique while lipofection is liposome-mediated gene transfer (Gavanji, 2013).

The transformed cells are grown into transgenic plants under stringently controlled conditions. The resulting plants are validated for their characteristics and cultivated in small-scale outdoor field trials before moving to larger scale cultivation. The methods of protein production applied includes the following:

- 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 transprotein is secreted into the medium and recovered (Thomas et al., 2002).

A European Union - South Africa project, Pharma-Planta (EU Sixth Framework Programme Integrated Project) aimed at developing a regulatory framework with strategies for commercial production of pharmaceutical proteins in plants. This project has reported successful production and purification of an HIV-neutralizing human monoclonal antibody 2G12 manufactured in transgenic tobacco plants (Pablo, 2010; Kisung & Koprowski, 2005).

Most biopharming applications target the production and storage of the PMP in the seeds, which are the natural plant storage organs. Dry seeds are easy to transport to a facility where the PMP will be extracted and processed. Therefore, a seed-specific promoter sequence will be transferred to the host plant alongside the gene itself and the selection marker. The most commonly used seed-specific promoters are the beta-phaseolin of the Bean (*Phaseolus* spp.) and the oleosin of *Brassica* species (Abiri et al., 2015). Plant-made pharmaceuticals are however produced in many different plants, including Maize (*Zea mays*), Tobacco (*Nicotiana tobaccum, N. benthamiana*), rice (*Oryza sativa*), Potato (*Solanum tuberosum*), Sweet potato (*Ipomoea batatas*), Sunflower (*Helianthus annuus*), Soybean (*Glycine max*), sugar cane (*Saccharum* spp.), Alfalfa (*Medicago sativa*), carrot (*Daucus carota*) and Tomato (*Lycopersicum esculentum* or *Solanum lycopersicum*) (Ahmad, 2014; Mohanty & Kumar, 2013; Fitzgerald, 2003; Shama & Peterson, 2008; Cogburn et al., 2007). Knowledge of a plant's agronomic and physiologic characteristics, and the pests and diseases to which it is prone, is an advantage in developing a production system. The best host plant, from an environmental point of view, is a non-food crop that does not have wild relatives in the vicinity. However, food plant hosts have the advantage that the PMP could readily be consumed by the patient.

3.5 Genetically Modified Drugs

Over the past two decades, genetically modified drugs have been developed and approved to mass-produce high and specific activity drugs like Insulin, Growth hormones, Follistim (for treatment of infertility in women), Human albumin for blood plasma, Monoclonal antibodies, anti-hemophilic factors, Interleukins and vaccines. These medicines are proteins generated using recombinant DNA technology (grown in bioreactors where protein is isolated & purified) through viral or bacterial transfection. Genes for proteins to be used in (human and animal) medicine can be inserted into plants and expressed by them (Yao et al., 2015). By 2011, more than twenty PMF pharmaceuticals had been placed in preclinical or clinical trials and several others commercialized as research and diagnostic reagents. In May 2012, the first PMF-derived recombinant enzyme, taliglucerase alfa, was approved for human use by the FDA (Kwong et al., 2011). This carrot cell produced enzyme is used in

replacement therapy to treat adult patients with Gaucher's[1] disease, a rare genetic disorder mostly found among Ashkenazi Jews. A drug called ZMapp produced in tobacco leaves was used to combat the 2014 Ebola virus outbreak in Liberia. By October of 2014, seven infected patients who received early treatment with the drug recovered while one who received late treatment with the same a month later died. The drug was subjected to clinical Phase I and 2 trials in 2015, and on 15 September same year, it was granted a fast track status by the FDA (Kwong et al., 2011).

3.6 Plant Made Pharmaceuticals (PMPs)

The classes of proteins produced in plants for molecular farming purposes can be categorized into four broad areas as:

- Parenteral therapeutics and pharmaceutical intermediates
- Industrial proteins (e.g., enzymes)
- Monoclonal antibodies (MAbs)
- Antigens for edible vaccines (Thomas et al., 2002).

Parenteral therapeutics and pharmaceutical intermediates

These include all proteins used directly as pharmaceuticals along with those proteins used in the making of pharmaceuticals. The list of such proteins is long, growing, and includes such products as thrombin and collagen (therapeutics), and trypsin and aprotinin (intermediates). Products in this class are generally manufactured under stringent cGMP (current good manufacturing practices) procedures and are of high purity. MAbs can also be classified in this group but are described separately due to their uniqueness (Thomas et al., 2002).

Industrial proteins (enzymes)

They are mainly the hydrolases (both glycosidases and proteases) and oxido-reductase enzymes such as laccase, a fungal enzyme used in fiber bleaching and bioglue of wood products. Enzymes involved in biomass conversion to produce ethanol can be considered to belong to molecular farming since they are usually in very large quantities and must therefore be produced very inexpensively (Thomas et al., 2002).

Monoclonal antibodies (Plantibodies)

They include antibody forms (IgA, IgG, IgM, secretory IgA, etc.) and antibody fragments (Fv) and can be produced in plants in both glycosylated and non-glycosylated forms. This class of therapeutic proteins is becoming increasingly important. Trastuzumab (Herceptin®), a humanized MAb for breast cancer treatment, became the first drug designed by a biomolecular engineering approach and was approved by the FDA. Trastuzumab is also being studied for the treatment of other cancers. It has been used with some success in women with uterine papillary serous carcinomas (Anon., 1987; Fu et al., 2010). To date, more than 15 MAbs have been approved by the FDA, and they are the fastest growing segment of the pharmaceutical industry (Fu et al., 2010). These plantibodies have the potential of improving productivity of new MAb products attempting to reach the marketplace. Examples of plant-derived MAbs in product development include a-caries for prevention of dental decay and a-herpes for prevention of herpes transmission (Barzegari et al., 2014).

Recently, a recombinant monoclonal antibody for rabies Post-exposure Prophylaxis was produced in transgenic plants. This is very helpful considering the worldwide shortage of anti-rabies immunoglobulins derived from immunized horses and humans, as well as the risk of adverse reactions associated with equine anti-rabies immunoglobulin (ERIG) and the high cost of human anti-rabies immunoglobulin (HRIG), have hampered efforts to reduce the number of human deaths from rabies exposure (Abiri et al., 2015).

Antigens for edible vaccines

These are specific protein antigens produced in plants and that will induce a humoral immune response when eaten by an animal or human. Protection studies have shown that they offer good efficacy when used, sometimes even more efficacious and cost effective than the commercially available vaccines (Thomas et al., 2002; Fu et al., 2010). Vaccines have been produced in plants for *Vibrio cholerae*, enterotoxigenic *E. coli*, hepatitis B virus, Norwalk virus, rabies virus, human cytomegalovirus, rotavirus and respiratory syncytial virus. Edible vaccines have been expressed in tomatoes, bananas, carrots and potatoes (Kwong et al., 2011). A therapeutic vaccine for protection against insulin-dependent autoimmune mellitus diabetes has been produced using insulin expression in plants. A personalized cancer vaccine has been produced in tobacco leaves for the treatment of lymphoma. As of April 2012, the only protein to receive an approval for human consumption was glucocerebrosidase which is synthesized by transgenic carrot cells grown in tissue culture. Many plant-derived antigens have also been purified and formulated for injectable delivery; however, oral delivery of some of these vaccines within food has also been successful (Thomas et al., 2002; Fu et al., 2010).

[1]In this disease, glucocerebroside (a sphingolipid, also called glucosylceramide) accumulates in cells and certain organs, and is characterized by bruising, fatigue, anemia, low blood platelet count and enlargement of the liver and spleen. The glucocerebroside accumulation is due to hereditary deficiency of the enzyme glucocerebrosidase (also known as glucosylceramidase), which metabolizes glucocerebroside.

3.7 Advantages of plants as Drugs Production Systems

The production of plant-made pharmaceuticals (PMPs) has many potential advantages relevant to clinical medicine. First, the cost of PMF-derived products is only 0.1% of mammalian cell culture systems and 2%–10% of microbial systems (Kwong et al., 2011). Secondly, the technology is already available for harvesting and processing plants and plant products on a large scale. Third, the purification requirement will be unnecessary when the plant tissue containing the recombinant protein is used as a food (e.g. for edible vaccines). Antigens can be produced in a number of plants. Bananas are currently said to be the best vehicle for hepatitis B vaccine, for instance, and could replace the injectable form of this vaccine, which is currently made in yeast. This could come in very handy considering the estimated 686,000 annual deaths from HBV, with some 3·61% of the global population living with chronic HBV infection (Shama & Peterson, 2008). Maize is also a suitable vehicle for orally administered, cloned vaccine antigens and other pharmaceutical proteins because it is capable of being processed into several palatable forms. Edible vaccines would not only be cheaper, but do not require a needle for administration. Clean, sterile needles are often in short supply where a healthcare infrastructure is lacking. Another advantage is that edible vaccines do not need refrigeration and are easy to store in a tropical climate (Ahmad, 2014).

Fourth, plants can be directed to target proteins into intracellular compartments in which they are less degraded hence more stable (Thomas et al., 2002), or even to express them directly in certain compartments (chloroplasts). Fifth, an advantage for using seeds or tubers is their ability to be stored for long periods. Besides, the specialized storage compartments in seeds help in reducing protein degradation, and in avoiding the exposure of the recombinant protein to phenolic compounds (Ahmad, 2014).

Sixth, molecular farming in plants has the potential to provide virtually unlimited quantities of recombinant proteins for use as diagnostic and therapeutic tools in health care and the life sciences. Plants produce a large amount of biomass and protein production can be increased further by using plant suspension cell culture in fermenters, or by propagation of stably transformed plant lines in the field (Ahmad, 2014). The amount of recombinant product that can be produced approaches industrial-scale levels (Shama & Peterson, 2008; Sack et al., 2015).

Seventh, PMP growth is not limited to special manufacturing facilities and can easily be scaled up to meet increased and varied market demands. For development of new therapeutic proteins, the capital risk associated with a commercial facility can be greatly minimized not only by the reduced amount of capital required but perhaps, even more importantly, by the delayed timing of the capital spending decision. This is because conventional facilities require five to seven years to build and validate whereas PMP facilities are relatively simple and can be built and validated in two to three years (Sack et al., 2015). Plant production is a cleaner method of producing a protein for drug manufacturing because plants are free of mammalian and avian infectious agents hence health risks arising from contamination with potential human pathogens or toxins are minimized (Abiri et al., 2015).

Going forward, biopharming is expected to be a major area of economic growth in agricultural biotechnology and pharmaceutical enterprises (Ahmad, 2014).

3.8 Disadvantages of plants as Drugs Production Systems

Lingering uncertainties regarding the potential benefits and hazards of biopharming include: cost-effectiveness in relation to competing platforms, unresolved technical problems, patent and regulatory issues, potential risks to human health, issues of gene spread, and animal-welfare concerns (Breyer et al., 2009). There are also a number of challenges and risks associated with their cultivation e.g. cross-pollination with nearby food crops of the same species. This poses a real risk of animals and people consuming harmful amounts of pharmaceuticals. This can be resolved through: isolation of the PMP crop location, the PMP being grown at a different time of the year, using male sterile varieties of the PMP, removing their tassels before the plants produces their pollen. Other risks include the presence of these pharmaceuticals in soil, altering the community of microbes living there. There are also potential dangers to those tending or harvesting the crops through exposure to PMPs. Finally, the drug product itself could become contaminated if the plants are sprayed with toxic pesticides (Breyer et al., 2009).

Current methods of production of such recombinant proteins in controlled environments faces several logistic, scientific and regulatory challenges throughout the system. These include generation of stable plant lines; master and working seed banks; reproducible cultivation and harvesting conditions; and downstream steps like efficient extraction of soluble proteins from plant biomass, extract clarification and host cell protein removal (Kisung & Koprowski, 2005). Researchers are therefore unable to control variations in the amount of pharmaceuticals produced in each plant species, in different plant parts, and even between subsequent generations. It is, therefore, nearly impossible to accurately quantify the appropriate dosage of edible vaccines. Besides, patients can develop immune tolerance after oral administration of edible vaccines, which may also be degraded in the digestive system. All these factors have greatly restricted the clinical use of edible vaccines (Kermani, 2006).

Most therapeutic proteins are glycoproteins, and *N*-glycosylation is often crucial for their stability, folding, and biological activity. Despite the advantage of plant cell glycosylation machinery over bacterial systems with respect to glycoprotein expression, glycan structures generated by plants and animals differ. Plant glycans contain (1,2)-xylose residues and (1,3)-fucose residues linked to the proximal *N*-acetylglucosamine, which are absent in mammals. The altered glycan structure in plants can potentially change the activity or longevity of antibodies, compared with their mammalian-derived counterparts. The potential allergic responses against plant-specific glycans might hamper plant production of MAbs, even though these glycan residues are present in all normal plant glycoproteins found in the human diet (Ahmad, 2014; Barzegari et al., 2014).

3.9 Regulatory Control of Biopharming

Cultivating plants to manufacture drugs involves many controls and regulations. Such controls are necessary to address concerns about genes for drugs mixing with crops and entering the food supply chain and their potential impact on the ecosystem.

A commercial biopharming operation in New Zealand would require Environmental Risk Management Authority (ERMA) approval. Full commercial release means that the product requires no controlling or monitoring. Conditional release, as for commercial biopharming operation, allows a new organism to enter the environment under certain specified management and/or monitoring conditions. The controls may affect who can own a biopharm operation, the type of farming operation that can be implemented, and identification of knowledge that may be relevant to assessing the practicality, risks and likely effects of the conditions (Breyer et al., 2009).

The USA has an institutional structure for regulating biotechnology products called the Coordinated Framework for Regulation of Biotechnology created in 1986 (http://usbiotechreg.nbii.gov). For PMF, the USA's Animal and Plant Health Inspection Service (APHIS) is the main agency involved in the regulatory process pertaining to the cultivation while the Food and Drug Administration (FDA) covers the pharmacological and safety aspects when the end product is a pharmaceutical. The GM plants are highly regulated by APHIS, meaning that the use of such plants outside a registered field requires authorization. For most GM plants, this authorization is obtained through a “notification” procedure. However, with regard to GM plants producing pharmaceutical and industrial compounds, APHIS has adopted strengthened regulatory requirements since 2003 (Aldridge, 2013). A more constraining "permit" procedure is applied, with specific confinement measures, procedures to verify compliance and ways to enhance the transparency of the permitting system (Aldridge, 2013).

Regulations in Europe are overseen by the European Agency for the Evaluation of Medicinal Products (EMEA). These regulations are similar to those found in the United States but are subject to individual member country regulations (or restrictions) as well. Additionally, to market any medicinal product containing active biological substances that have been manufactured using transgenic plants in the European Union, companies must use a centralized application procedure (Sack et al., 2015). The EMEA requires a vast amount of information to be presented in applications to produce PMPs. This includes justification for the choice of host plant; characterization of the heterologous gene; a description of the expression construct and a characterization of the final construct map; description of materials, procedures, and methods used in plant transformations; a rigorously characterized master cell bank; a global strategy description that includes relative parameters characterizing the expression construct, the plant, and the genetic stability of the production system; and detailed characterizations of expression constructs and final purified proteins, including nucleic acid and expressed protein analysis and validated methods for analysis (Sack et al., 2015).

It is noteworthy that in biopharming the plant represents only one step in a complex, multi-step pharmaceutical production process. Consequently, most processes in the production of pharmaceuticals will follow traditional regulatory requirements regardless of whether the proteins are produced using plants or other methods. Stringent GMP and GAP practices are required and are meant to ensure containment of the transgenic crop and prevent contamination of wild or domestic plants in addition to providing consumers with a safe product. The potential societal and ethical issues linked to plant molecular farming are also of considerable interest, and so too are their quality, purity or efficacy (Aldridge, 2013; Sack et al., 2015; Rivera et al., 2012; Buyel & Fischer, 2014).

4. CONCLUSION AND RECOMMENDATIONS

African perspectives on genetically modified organisms need to focus on science and learning in general in helping equip Africans to make informed decisions on scientific matters. Not only on GMOs but on other technologies as well. This approach means making a generational commitment to improving scientific capacity in Africa through investments in universities and other institutions of learning. Ultimately, GMOs are just one of many potential methods of increasing African productivity. Interventions, such as the ones in the USA and Europe, should align with the national priorities of individual countries, which may or may not embrace GM technologies.

There should be immense investments in locally relevant research and development capacities. As science and technology issues become increasingly complex, African countries will need a strong cadre of professionals with a firm footing both in the scientific arena and in the local development realities that confront their nations. In building the next generation of African scientists, African Universities should be empowered to play a greater role in applied research and development and to connect more effectively with national development priorities, with farmers and with local communities.

Regional groupings such as the East African Community (EAC), COMESA, SADC and ECOWAS, should formulate policies and agreements to harmonize national bio-safety policies. This will inspire the intraregional trade and consider cross-border trade in maize and other foods. As individual African countries move to commercialization of GM crops, movement of food within regional economic groupings will become more complex and require greater harmonization of bio-safety standards and stronger monitoring and enforcement capacities.

Pharmacists need to appreciate the huge responsibility that comes with biopharming and, especially, the need for stringent professional, ethical and regulatory controls. There is a lot of money to be made in the genetically modified drugs market but people still pay the high prices of other drugs that have been found to be ineffective and also kill patients quicker. Some Drugs administrations ignore long-term risks that come with genetically modified drugs and instead release them to the public to boost sales, without having the necessary testing done.

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