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Review Paper

Genetically Modified Crops: A Reality Check and Present Global Scenario

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Abstract: Genetically modified (GM) crops have failed to be the popular success, the scientists claimed them to be, few decades back. Most concerns about GM foods fall into three categories *i.e.* environmental hazards, human health risks, and economic concerns. While the human health issues are of utmost importance, as they directly impact the future of such crops, the environment and economical issues are deriving support in present day society that is well informed and aware of the concept of coexistence and harmony between all prevalent biotic as well as abiotic factors. Long term environmental and health monitoring programs in favor of GM plants either do not exist or are inadequate to convince the masses. There is a growing concern that introducing foreign genes into food plants may have an unexpected and negative impact on human health. Most of the animal feeding studies have revealed a mixed interpretation, means some claim that the GM crops code for the known proteins in the transformed host and that they should straight forward be regarded safe, while others are of the opinion that genes do not always encode a fixed three dimensional protein structure. The term 'intrinsically disordered protein' has been introduced to describe proteins that lack a fixed three dimensional structure. It has been reported that 33 percent of eukaryotic proteins contain disordered segments. This may result in allergenicity by them, in its multi faceted form which may be the possible cause of various harmful health effects. Besides, there are evidences that GM crops are sometimes ill adapted to the challenges facing global food and agriculture systems, and have failed to materialize outside the laboratory, or have unraveled when faced with the real world complexities of agricultural ecosystems, and needs of farmers. Environmental hazards also include the unintended harm to other organisms. Non GM advanced methods of plant breeding are already delivering the sorts of traits promised by GM crops, including resistance to diseases, flood and drought tolerance. GM crops are also supposed to restrict innovation due to intellectual property rights owned by a handful of multinational corporations. Nevertheless, genetic engineering, beyond doubt is the inevitable wave of the future and we cannot

afford to ignore this technology that has such enormous potential benefits. However, all must proceed with caution to avoid causing unintended harm to human health and the environment as a result of our enthusiasm for this powerful technology. This paper deals with the issues of looking at GM plants with a critical and analytical outlook, so that the myths and over expectations of populations worldwide, could be mitigated, besides, doubts as well as fears regarding their uses be tackled and answered.

Keywords: Genetically Modified Crops, GM Foods, Transgenics, Genetically Modified Organisms, Nutritionally Superior Foods, Health and Safety Concerns, Animal Toxicity, Environmental concerns, GM Industry, Multigenerational Feeding Studies.

Abbreviations: Genetically Modified Crops (GM Crops), Genetically Modified Organisms (GMOs), Biotechnology Derived Foods (BD Foods).

INTRODUCTION

Genetically modified (GM) crops have not been able to deliver, the benefits that were promised and promulgated by the researchers worldwide, or in other words, this amazing horizon of biotechnology has not been translated into tangible products with direct benefits to the society and consumers. One can point out multiple reasons, ranging from technical issues related to ill effects from toxicity to genetic pollution to bio piracy issues, and also the social issues, including their acceptance by traditional societies in light of their informed fears, doubts and wide ranging apprehensions that are possibly hard to address, if not impossible. Although, the real reasons may be there to decipher and deliver, but the fact is that the promises have grown, rather accumulated over the last two decades but their popularity in terms of fulfillment has not (Ludlow, 2012; Klaus, 2014). Despite twenty plus years of pro GM marketing campaign by powerful industry lobbies, supported by several scientific documentations in their favor, GM technology and its products have only been taken up by a handful of countries, that too for a handful of crops. Figures and data generated from the worldwide GM industry indicate, that only five or so, countries account for 90% of global GM cropland, and nearly all of these GM crops, if not all, do belong to either herbicide tolerant or pesticide producing plants (Prakash, 2001; Puchta and Fauser, 2013). Meanwhile, rest of the regions of the world have resisted or have been quite hesitant in accepting them. Further, most European consumers do not prefer consuming GM foods, and only a single type of edible crop, GM maize, is cultivated there (Campbell, 2002). Major part of Asia is GM free, with the GM acreage in two large agricultural countries, *i.e.* India and China mostly accounted for by a non food crop *i.e.* cotton. Only three countries in Africa grow any GM crops. In other apparent and precise words, GM crops are not 'feeding the world' as was claimed to do so at the dawn of twenty first century (Kiple and Ornelas, 2000; Schubert, 2002; Lotter, 2008).

What are Genetically Modified Crops?

Genetic manipulation is not new, for millennia, farmers have relied on selective breeding and cross fertilization to modify plants and encourage desirable traits that improve food production and satisfy other human needs (Horsch, 1985). Later, need dictated scientific intervention and adoption of technological advancement in the domain of biology paved the way for the astonishing technology, that we call today biotechnology (Williamson, 1991; Dale, 1999).

Biotechnology includes a wide range of scientific techniques that are used in several fields including agriculture, industry and medicine. The Convention on Biological Diversity (CBD) defines biotechnology as, 'Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use' (Rommens, 2004, Rommens et al., 2007). Agricultural biotechnology includes several aspects as biofertilization, tissue culture, marker assisted plant breeding and transgenics. Several examples can be quoted for such uses, like domestic and industrial artisans have exploited traditional fermentation techniques to transform grains into bread and beer, and milk into cheese and other dairy products, which have tremendous economic value. Such intentional modification of the natural world has contributed enormously to human well being and cultural, social as well as economic prosperity (Waltz, 20012). Transgenic applications of biotechnology are relatively recent and these involve the modification of the genetic makeup of an organism through the insertion of a gene from another organism and has been used to modify plants, animals and microorganisms. A gene is a biological unit that determines an organism's inherited characteristics including its size, shape, activities, metabolism, its response towards external conditions and what not? This process of modification is known by various names such as transgenics, genetic recombination, genetic engineering and also recombinant DNA technology. It aims at adding characteristics that the original organism did not have. The resultant organisms are called 'genetically modified' (GM) or 'genetically engineered' or 'living modified organisms' (LMOs), these organisms have been genetically modified in a way that does not occur naturally (Freese, 2004; Rollin, 2011).

The last few decades have witnessed a revolution in transgenics, also kept under plant or agriculture biotechnology, which has impacted the experimentation in the agriculture by the application of the tools of molecular biology to plant breeding and crop cultivation. This era of transgenics may be divided into two phases or generations, the first phase has largely focussed on input traits that benefit mainly the cultivator *i.e.* the farmer, who suffers huge economic losses due to prevailing biotic or abiotic stress factors. Examples of such GM crops, to combat these stress factors include, the introduction of genes for insect resistance and herbicide tolerance, which reduce losses due to pests and weeds, as well as the quantity of chemical applications during their cultivation (Truninger, 2013). The outstanding success of these engineered crops is evident from the fact that the area of farmland devoted to transgenic crops has grown from a negligible acreage 10 years ago to well over half the acreage for major crops in agriculturally important advanced countries such as USA, Canada and Argentina (Waltz, 20012). The second phase of transgenics, that deals with output traits, which directly benefit the consumers in a multitude ways, and shall eventually become prominent in the practice of GM technology. Several desirable output traits including prolonged shelf life of fruits and vegetables, that are highly resistant to rotting by bacterial and fungal infections, nutritionally superior foods, such as the vitamin A enriched 'golden rice' or tropical oils that are unsaturated, and agricultural products of medicinal value, such as single or multivalent edible vaccines are being worked upon and are in various stages of development (Daniell et al., 2001; Liu et al., 2012). A long lasting acceptance of genetically modified crops by world population and societies might well depend upon the emergence of this second phase of transgenics under plant biotechnology.

Nevertheless, plant biotechnology has been around for over thirty years, its tools and techniques can transfer genes from one organism to another, to introduce a new trait into a plant in a targeted and controlled manner. For example, insect resistant GM cotton uses a gene from a naturally occurring soil bacterium, *Bacillus thuringiensis* to provide the cotton with built in insect protection by means of the toxin producing gene, that could kill the insect feeding upon it. Further, genetic modification does not necessarily mean that a gene from another organism has to be used to create the genetically modified organisms (GMOs), at times it can, also mean that the organism's own genes could be subjected to some change for any underlying benefit (Jones et al., 1990). In 1973, Stanford biochemist Paul Berg and colleagues created the first ever recombinant DNA molecules by joining fragments of DNA molecules from diverse organisms, creating a molecule that shared properties from both the original fragments. This set the scene for the creation of transgenic organisms (Jackson, et al. 1972). Fuelled by this research and several other related inventions, scientists designed the blue prints over which the foundation of transgenic / genetically modified organisms (GMOs) including GM plants was laid down (Funatsuki et al., 1995; Maximova et al., 1998). In 1994 the United States Food and Drug Administration approved the first commercially available transgenic fruit the Flavr Savr tomato (also known as CGN-89564-2) for marketing. The plant was modified to slow down the tomato's ripening process after picking. In 1996, Monsanto commercialised herbicide resistant soybeans, known as 'Roundup Ready', followed by alfalfa, corn, cotton, spring canola, sugar beets and canola (Kiple and Ornelas, 2000; Schubert, 2002).

The main tools initially used to introduce DNA into plants were the biolistic methods, which inject DNA bound to tiny particles of gold or tungsten cells into plant tissue or cells under high pressure (Harwood, 2000). These low targeted methods were later followed by the use of *Agrobacterium tumifaciens*, a bacterium with the ability to transfer genes into a plant host (James et al., 1990; De Bondt et al., 1994). All transgenic crops that are currently commercially grown have been produced using these methods. This has been effective with simple traits such as herbicide tolerance and insect resistance (Vasil et al., 1992). However, the random nature of gene insertions might have undesirable effects, and these methods are not favourable for making combined trait changes (Reddy and Thomas, 1996).

Future advances in GM crop technology may equip scientists with new and sophisticated biotechnology tools and methods that shall offer precise genome editing by site specific integration, deletion and mutation of genes and are expected to have a great effect on plant biotechnology (Latham et al., 2006). The genome is modified using artificially engineered nucleases. A nuclease is an enzyme capable of breaking the phosphodiester bonds, which are strong bonds between the subunits of nucleic acid. The nuclease creates specific double stranded breaks at desired locations in the genome, which previous methods were unable to do. Zinc finger nucleases (ZFNs) and transcription activator like effector nucleases (TALENs) target unique sequences within complex genomes and are used to edit the genome *in situ* (Shukla et al., 2009; Townse, et al., 2009; Wood et al., 2011). The CRISPR/Cas system performs targeted, highly efficient alterations of genome sequences (Pattanayak et al., 2011; Shen, 2013).

Expected Benefits and Why GM Crops

The world population has topped seven billion and is predicted to double in the next 50 years. Ensuring an adequate food supply for this booming population is going to be a

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major challenge in the years to come. Not only was this technology supposed to make food and agriculture systems more efficient, simpler, safer, but GM crops have constantly being touted as the key to feed the exponentially growing population of world and fight climatic changes by producing strong, resistant crops, best suited for growing in harsh conditions (Fischer et al., 2014). As food security has been a high priority for governments and communities around the world specially the developing and third world countries. Although, developed countries do not have a problem feeding their population, food security in these countries has been linked to the political stability of the region, consumption, trade, climate and environmental challenges that may affect food production.

The Food and Agriculture Organization (FAO) of the United Nations defines food security as 'when all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life'. A recent report states that about one in eight people in the world suffers from chronic hunger and are unable to get access to enough nutritious food to live an active and healthy life. Besides, hidden hunger, *i.e.* the short supply of essential nutrients in the food and its impending repercussions on the overall health and productivity of the population has also been a growing concern (Truninger, 2013). Improvements in food security by measures including increasing crop yield, improving agricultural practices, reducing waste, pre and post harvest losses, changing diets and expanding aquaculture shall require multidisciplinary cooperation and extensive execution (Godfray et al., 2010).

Further, genetically modified crops alone may not solve the problem of food insecurity, but they do have the potential to play an important role in a broader food security strategy, they promise to meet this need in a number of ways (Rotman, 2013):

1. Pest resistance: Crop losses from insect pests have been reported to be staggering, resulting in direct devastating financial losses for farmers and indirect starvation in developing countries. Farmers typically use several tons of chemical pesticides annually, and aware consumers do not wish to eat food that has been treated with pesticides because of potential health hazards. Run off, of agricultural wastes from excessive use of pesticides and fertilizers is responsible for poisoning the water supply, causing harm to the environment. Growing GM foods such as Bt crops may help eliminate the application of chemical pesticides and reduce the cost of bringing a crop to market (Dale, 1999).
2. Herbicide tolerance: For several crops, it is difficult and not cost effective to remove weeds by physical means like tilling, therefore, farmers usually spray large quantities of different herbicides (chemical weed killers) to destroy weeds, a time consuming and expensive process, that requires care so that the herbicide doesn't harm the crop plant or the environment. Crop plants genetically engineered to be resistant to one very powerful herbicide could help prevent environmental damage by reducing the amount of herbicides needed, provided the weeds do not obtain this resistant gene from crop plants by horizontal gene transfer to convert themselves from herbicide sensitive to herbicide resistant weeds (Schulz et al., 1990; Rubin, 1991).
3. Disease resistance: There are many viruses, fungi and bacteria that cause

plant diseases resulting into tremendous economic loses. Plant biologists are rigorously working to identify the pathogenesis of the diseases and create transgenic plants with genetically engineered resistance against these diseases (Korte et al., 1994; Dahleen et al., 2001).

4. Cold tolerance: Unexpected climatic cold or frost may destroy sensitive seedlings. An antifreeze gene from cold water fish has been introduced into experimental plants such as strawberry, tobacco and potato. With this antifreeze gene, these plants are able to tolerate cold temperatures that normally would kill unmodified seedlings (Firsov and Dolgov, 1999).
5. Drought/temperature/salinity tolerance: As the world population is exponentially growing and more land is being utilized for housing instead of food production, farmers will need to grow crops in locations previously unsuitable for plant cultivation. Creating plants that can withstand long periods of drought or high salt content in soil and groundwater will help them to grow crops in once inhospitable places (Liu et al., 2012; Hakata et al., 2012).
6. Enhanced nutrition: Malnutrition is common in third world countries where impoverished population rely upon a single crop like rice as the main staple food in their diet. However, rice is deficient of adequate amounts of all necessary nutrients to prevent malnutrition. If rice is genetically engineered to contain additional vitamins and minerals, nutrient deficiencies could be alleviated. For example, blindness due to vitamin A deficiency is a very common problem in third world countries. Researchers have created a strain of 'golden' rice containing an unusually high content of beta carotene which is the precursor of vitamin A (Ye et al., 2000). Plans are underway to develop golden rice that also has increased iron content to mitigate iron deficiency in rural and under privileged population that do not have access to other iron sources as green vegetables, fruits and nuts.
7. Pharmaceuticals: Medicines and vaccines often are costly to produce and sometimes require special storage conditions not readily available in third world countries. Researchers are working to develop edible vaccines in tomatoes and potatoes. These vaccines will be much easier to ship, store and administer than traditional injectable vaccines, a plant biotechnological innovation that might have important public health implications. Vaccinogens can be expressed either from plant viral vectors or as transgenes. In the former case, the vaccinogens need to be purified from the virus infected plants, whereas in the latter case, transgenic plant organs expressing vaccinogens can be consumed directly with the hope that they will act as oral vaccines to confer immunity. So far, at least seven antigens from various animal and human pathogens have been successfully expressed in plants and, in several cases, initial results indicated that they are able to elicit mucosal immune responses. Future challenges include the design of vaccinogens so that these can be protected from digestive enzymes in the gut to make them more effective in providing immunity (Daniell et al., 2001).
8. Phytoremediation: Contrary to their application, not all GM plants are grown as crops. Soil and groundwater pollution continues to be a major problem in all parts of the world. Plants such as poplar trees have been genetically engineered to

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clean up heavy metal pollution from contaminated soil (Ahmed and Focht, 2000).

Of course, the technology has the potential to increase crop yield, food quality and nutrient composition at multiple levels, but crops produced through GM technology continue to be a subject of controversy (Pusztai et al., 2003). This is partly because of the perception that modifying plant genes is a newly discovered phenomenon, when in fact humans have been breeding and selecting crops for 10 000 years, since, the ancient man adopted the practice of crop cultivation. Although, traditional practices relied upon extensive breeding and selection of superior traits, rather than mixing the genes in laboratory (Schubert, 2002). Besides, Different GM crops include different genes inserted in different ways. Individual GM crops and their safety has to be assessed on a case by case basis and it is not always possible to make general statements on their safety. Despite the strongly positive track record of biotechnology derived crops for farmers, consumers, and the environment, unexploited opportunities for additional as well as widely shared benefits are considerable and still a matter of extensive research and development (Qaim and Janvry, 2003).

Major Concerns and Societal Activism

Attitudes towards technology play a crucial role in its acceptance by the public, uptake by concerned industry, and the level of intervention by government, which in turn may have an impact on its adoption, adaptation, development and its use in innovation. Besides, our beliefs, and perceptions of risk, heavily influence our opinions about new technologies, which is also true with GM crops (Rodriguez and Ordonez, 2013). Despite huge scientific evidences, there are still concerns that the introduction of genetically modified crops to the food chain may harm the environment as well as human health, and shall badly impact the livelihoods of farmers, in particular those in developing countries. Social activists, worldwide point out towards the impending potential for food industry monopolies, where a small number of multinational corporations may control an increasing share of global agricultural supply and distribution (Robinson et al., 2013). As a result of public concern, governments and regulatory authorities have been cautious in their approach towards regulating GM crops. Further, regulation is heavily influenced by the process of cultivation and consumer attitudes, instead of assessment of crop traits, scientific evidence as well as underlying risks and benefits (Horton, 1999).

In 1942, J.I. Rodale said, 'One of these fine days, the public is going to wake up and shall pay for food and eatables including, fruits, vegetables, meats, etc., according to how they were produced.' Albeit, this has been a slow pace movement, the interest in this regard has been growing in leaps and bounds, and that day has finally arrived. With the growing health concerns and awareness, more and more people have understood that food matters, and its implications on long term health can't be over ruled, because right food is not less than medicine (Magnusson et al., 2002).

The reasons for such disappointment in the acceptability of GM crops may lie in the close and detailed critical studies in various parts of world that have not been encouraging and some have even shown a dismal picture. Till date, no GM crops have been designed to deliver the motive of higher yields. Few instances, where yields have been enhanced, the crop to which a GM trait has then been added, have tended to come not from GM technology, but from the high quality varieties created through conventional breeding which was used to create a GM crop. Therefore, it is apparent beyond doubt that GM pesticide producing crops for example can only increase yields temporarily by reducing losses to pests in years of high pest infestation (Domingo, 2007).

The release of GM crops into the environment and their rigorous marketing has resulted in a public debate in many parts of the world. Even though, the issues under debate are usually very similar (costs, benefits and safety issues), the outcome of the debate differs from country to country (Altieri and Rosset, 1999). Environmental activists, religious organizations, public interest groups, professional associations scientists and government officials have all raised concerns about GM crops, and have criticized agribusiness for pursuing profit without much concern for potential hazards, and the government for failing to exercise adequate regulatory oversight (Zdunczyk, 2001). The safety assessment of GM crops generally focuses on issues like, direct health effects (toxicity), potential to provoke allergic reaction (allergenicity), specific components thought to have nutritional or toxic properties, the stability of the inserted gene, nutritional effects associated with genetic modification and any unintended effects which could result from the gene insertion (Dona and Arvanitoyannis, 2009; Domingo and Bordonaba, 2011). While on other miscellaneous issues such as labelling and traceability of GM foods as a way to address consumer preferences, there is no worldwide consensus till date (Miller et al., 2008; Martinelli et al., 2013).

Despite, above mentioned key attributes and hindrances in their progress, most concerns about GM crops and GM foods fall into three major categories *i.e.* environmental concerns, human health risks, and economic concerns (Chua and Sundaresan, 2000; Bulchandani, 2016).While the human health issues are of utmost importance, as they directly impact the future of such crops, the environment and economical concerns are no less important, as they are deriving support in present day society that is well informed and aware of the concept of coexistence and harmony between all prevalent biotic as well as abiotic factors. Long term environmental and health monitoring programmes either do not exist or are reported to be inadequate (Abdo et al., 2013). Independent researchers who have been trying to unearth facts, have time and again complained that they are denied access to material for research (Bawa and Anilakumar, 2013). Several such issues have been put forward and raised at various platforms globally and their solution in piece meals, if not in totality have been tried to address by the researchers, scientists and social activists (Nicolia et al., 2014).

Health and Safety Concerns

There is a growing concern that introducing foreign genes into food plants may have an unexpected negative impact on human health. Most of the animal feeding studies have revealed a mixed interpretation, that means a cluster of researchers claim that the GM crops code for the known proteins in the transformed host and that they should straight forward be regarded safe (Magana Gomez and Calderon, 2008; Zhang and Shi, 2011). Another cluster of researchers have claimed that each GM product must be tested for a variety of effects over a long period and multiple generations of the test animals (Krzyzowska et al., 2010; Hilbeck et al., 2015). Still others claim in their published research that some GM crops, when fed to animals, have exhibited harmful effects compared to non GM controls (Pusztai, et al., 1999; Taylor et al., 2007; Malatesta et al., 2008). These piece meal studies and their differing results have indicated that GM food and feed may cause some common toxic effects on hepatic,

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pancreatic, renal, or reproductive systems, altering the hematological, biochemical, and immunological parameters and thus should draw attention towards human health concerns (Vecchio et al., 2004; Finamore et al., 2008; Gab-Alla et al., 2012; El-Shamei et al., 2012). Majority of these studies are performed on animal models such as cows, sheep mice, fishes, and chickens (Trabalza et al., 2008; De Vendomois et al., 2009; Gu et al., 2013). The digestive systems and metabolic functioning of these animals differ significantly from those of humans. Thus these studies are unlikely to provide useful information on human health risks. Besides, there were no evidences of adverse effects of GM crops for many species of animals in acute or short term feeding studies, but serious debate still surrounds long term and multigenerational feeding studies. Long term multigenerational feeding studies are clearly necessary to further investigate this issue (Snell et al., 2012; Se´ralini et al., 2012).

As allergenicity, in its multi faceted forms, may be considered the most probable cause of various adverse effects, scientists have proved that a non allergenic protein in one food type can be transferred via its genes to another food type and become allergenic. Some pro GM crop scientists often took it for granted, that the transferred protein would behave as it did in its parental crop. It is now well understood that genes do not always encode a fixed three dimensional protein structure. The term 'intrinsically disordered protein' has been introduced to describe proteins that lack a fixed three dimensional structure. It has been reported that 33 percent of eukaryotic proteins contain disordered segments (Ward et al., 2004). Also, intrinsically unstructured proteins have been connected and correlated to a number of chronic diseases and malformations including various types of allergies. Therefore, studies are required to be undertaken to know whether, GM crops, through posttranslational modification, have a higher frequency of proteins that contain such disordered segments that might have certain health ramifications (Zolla et al., 2008).

The professional toxicologists have also issued a policy statement stating that the available scientific evidences indicated that the potential adverse health effects arising from biotechnology derived foods (BD foods) are not different in nature from those created by conventional breeding practices for plant, animal, or microbial enhancement, and are already known to toxicologists. However, it has also been added, that the methods have not yet been developed by which whole foods (as compared with single chemical components) can be fully evaluated for safety (Kok and Kuiper , 2003; Bøhn et al., 2014). Progress is also needed to be made in developing definitive methods for the identification and characterization of protein allergens, and this should currently be the major focus of research. While, rather optimistic about the safety of existing GM crops, the report of the Society of toxicology, has made it clear that the methods to test the food and the passive reporting system are deficient. The level of safety of current BD foods to consumers appears to be equivalent to that of traditional foods. The report further says, that verified records of adverse health effects have been absent, although, the current passive reporting system would probably not detect minor or rare adverse effects, nor can it detect a moderate increase in common effects such as diarrhea. However, this is no guarantee that all future genetic modifications will have such apparently benign and predictable results. A continuing evolution of toxicological methodologies and regulatory strategies will be necessary to ensure that this level of safety is maintained (Society of Toxicology, 2003).

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Advanced and precisely predictable as well as accurate methodology of testing may include a full range of 'omics' (molecular profiling analyse), *i.e.* genomics, transcriptomics, proteomics, and metabolomics along with profiling of siRNA (gene silencing RNA) and miRNA (microRNA) molecules should also be carried out, to look for intended and unintended changes brought about by the genetic engineering processes in GM crops (Ricroch et al., 2011). Unlike regular RNA molecules, which code for proteins, miRNA molecules regulate gene expression. These profiling tests must be done simultaneously on the GM and the isogenic nonGM crops grown at same location and time, in order to highlight the presence of potential toxins, allergens, and compositional/nutritional disturbances caused by the GM transformation (Catchpole et al., 2005; Nunes et al., 2013). There must be no spurious use of non isogenic controls, as is often done by industry in tests conducted for regulatory purposes (Prescott et al., 2005). Further, 'toxicokinetics' *i.e.* toxicokinetic analysis of the transgene derived pesticide must be performed, to find out what happens to it, once it enters the body of an animal or human that consumes or feed upon it. This includes tracing and tracking details of how and where it travels in the body, how it is broken down and into what products, how efficiently it is excreted, and to what extent and where it accumulates. The entire pesticide formulation as sold and used must be tested, and in the case of pesticide producing GM plants or herbicide tolerant GM plant, the pesticide or herbicide isolated from the GM plant must be tested, this should be tested taking along the entire GM plant to record the comparative analysis (Taylor et al., 1999; Hammond et al., 2004).

An additional and clinically significant cause for concern regarding GM food and feed is the potential presence of 'antibiotic resistant marker genes' in the GM crops. These genes have been deliberately included in the GM gene cassette to enable biotechnologists to observe whether, the gene of interest has been successfully integrated into the DNA of the cells of the host plant. When an antibiotic is added to the plant cell culture, only those cells that have successfully integrated the GM gene cassette into their DNA (*i.e.* transformed) are able to survive. If the antibiotic resistance marker gene is physically linked to the GM gene of interest, it persists in the final GM crop that is commercialized. In an *in vitro* study (laboratory study not performed in living animals or humans), GM Bt maize DNA was found to survive processing and was detected in the digestive fluids of sheep (Duggan et al., 2003). This raises the possibility that the antibiotic resistance gene in the maize or any other GM crop might be taken up and incorporated into the DNA of gut bacteria of the intended consumer, which is an example of horizontal gene transfer. If the antibiotic resistance gene transferred to a pathogenic bacterial species, this could result in antibiotic resistant disease causing bacteria (called superbugs) in the gut, thus making it a breeding ground for emergence of such devastating and potentially lethal superbugs (Bulchandani, 2014).

Lastly, there have been questions raised, whether any conflict of interest could be a factor in how the GMO health studies are executed and interpreted (Portier et al., 2014). In case of any negative results, they should be replicated by independent authorities or researchers, to see if they still persist and hold up to rigorous testing without any bias and influence. Until these, are replicated and shown to be false positives, all have an obligation to treat these studies with respect and concern. This point was made by the group of scientists who signed a joint statement that was published in Environmental Sciences Europe. The statement does not assert that GMOs are unsafe or safe. Rather the statement concludes that the scarcity and contradictory nature of the scientific evidence published to date prevents conclusive claims of safety, or lack of safety, of GMOs.Besides, it has been pointed out that many of these articles are written by GMO proponents and promote the view that GMOs are safe and adequately regulated or promote industry friendly approaches to safety assessment (Séralini et al., 2008; Diels et al., 2011).

Economic Concerns

The potential disruptive impacts of new technologies can at times be overestimated. One can find literature that both supports and refutes the economic benefits of genetically engineered crops to farmers (Lotter, 2008; Diels et al., 2011). In 2011, Berlin's Ecologic Institute reviewed 721 studies to provide an overview of economic performance of GM crops. The institute compared the performance of GM crops with that of conventional crops for yield, gross margin, seed cost, applied pesticide cost and labour/management costs (Seufert et al., 2012). The review of studies indicated that on average Bt cotton, a genetically modified variety of cotton producing an inbuilt insecticide, shows an economic advantage over conventional cotton. However, the results obtained were vastly different in different countries, mostly due to pest management practices. Countries with well established pest management, had lower yields but got benefits from reduced pesticide costs. Bt maize yield exceeded that of conventional maize in most countries, but the results were affected by the seasons and regions in which the crop was grown (Jose et al., 2012; Robinson et al., 2013).

Gene transfer to non target species of mass cultivation, is another concern. Crop plants engineered for herbicide tolerance and nearby weeds may cross breed, resulting in the transfer of the herbicide resistance genes from the crops into the weeds. These 'super weeds' might then become herbicide tolerant as well, rendering the GM crops ineffective and/or result into use of enhanced quantities of chemicals by farmers. Other introduced genes may also cross over into non modified crops planted next to GM crops. The possibility of interbreeding has been shown by the defense of farmers against lawsuits filed by certain multinational companies, that have filed patent infringement lawsuits against farmers, claiming that the farmers obtained licensed GM seeds from an unknown source and in a way they did not pay royalties. The farmers on the other hand claimed that their unmodified crops were cross pollinated from someone else's GM crops planted a field or two away. More concrete investigations and coveted research is needed to resolve this issue and steps must be formulated to prevent any such events for the acceptability of GM crops by poor and not so technically sound farmers (Graff et al., 2003; Stein, 2004).

In addition to their usual concern towards the health and environmental risks, those who oppose GM crops are passionate in their fight against large agricultural biotechnology companies, that are blamed for exploiting poor farmers and small farm owners who are forced to buy seeds each year, and are prohibited to legally save seeds from year to year. Supporters of GM scenario are puzzled if the technology is to be blamed for the business practices of large companies selling the products at their own terms. Opposition to the technology has resulted in an increase to the safety threshold expected of genetically modified crops (in comparison to conventionally bred crops). Unexpectedly, this has led to greater cost for the assessment, registration and use of the technology which discourages smaller

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competitors, reinforcing the oligopoly, if not the monopoly, that opponents are fighting against (Klaus, 2014; Wesseler and Zilberman, 2014).

For thousands of years farmers have saved the seeds of plants with desirable characteristics, this has been an integral part of agriculture and is a continuing practice for most farmers. Until recently seeds were not viewed as a commodity, and crop plant genetics were considered common property. Because of this, there was little investment in seed development and procurement, farmers did not need to buy seeds from year to year and could share seeds with each other (Stein, 2004). The seed industry has undergone significant changes since genetic information and resources which were once treated as public assets became subject to proprietary control. Although, patent protection is the need of the hour and is very much required to promote innovation, it also means that proprietary control is mostly owned by a few large companies because only they are in the best position to pay for expensive research and regulation costs. Besides, patent holders may license the seed to others for set fees and they may specify own license terms and conditions. Patent holders have the right to prevent others from producing or selling patented seeds for a period of 20 years (Waltz, 2009; Rowe, 2010).

In this era of molecular biology and diminishing biodiversity, the patenting of genetic information has been a controversial issue because genes are naturally occurring and have evolved during past thousands of years, therefore, should no way be treated as a commodity of trade. The earliest genetic patents were issued in 1982 in the US, which opened the door to patenting biotechnology discoveries. As stated earlier patents are issued and have been promoted to encourage innovation and provide protection to allow those investing in an innovation to secure the profit from their investment and innovation. Corporations claim they need product control while opponents claim that patenting gives corporations too much influence over a product that everyone needs. Thus, it is in the financial interest of large biotech companies to deny farmers the ability to save seeds from year to year, forcing them to buy the product new year after year (Waltz, 2010). Besides, many farmers are required to sign contracts that prevent them from legally saving GM seeds. The long and complex history of intellectual property rights and seed technology illustrates how political and business motives play an important role in deciding policy. But at the same time, strong intellectual property protection for GM seeds has been partly responsible for the rapid growth and development in new seed varieties (Stein, 2004; Michaels, 2008).

Environmental Concerns

There are issues regarding GM crops contaminating non GM crops and several hundreds incidents of GM contamination have been recorded globally (Dale, 1992; Quist and Chapela, 2001). Staying GM free imposes considerable additional, and sometimes impossible, costs for farmers. There are evidences that GM crops are sometimes ill adapted to the challenges facing global food and agriculture systems. Thus, the promises regarding long term benefits that have been made, have failed to materialize outside the laboratory, or have unraveled when faced with the real world complexities of agricultural ecosystems, and the real world needs of farmers. Environmental hazards also include the unintended harm to other organisms (Evenhuis and Zadoks, 1991; Losey et al., 1999; Pilcher et al., 2005; Hilbeck et al., 2012). Non GM advanced methods of plant breeding are already delivering the sorts of traits promised by GM crops, including resistance to diseases, flood and drought tolerance. GM crops are also supposed to restrict innovation due to intellectual property rights owned by a handful of multinational corporations (Schubert, 2002; Shelton et al., 2009).

Then there are studies that have reported the reduced effectiveness of transgenics, *i.e.* after a few years of their use, problems such as herbicide resistant weeds and super pests emerge in response to herbicide tolerant and insect resistant GM crops, resulting in the application of additional pesticides, which in no way is desirable and is against the very concept of biocontrol and biotechnology (Hoffman, 1990; Gatehouse et al., 2011). Patent law allows patent holders in some way to control and restrict independent research, which has led to inadequate testing of human and environmental health risks of GM products. These research restrictions can be interpreted as contrary to the public interest and inconsistent with the underlying principles of patent law. It is worth considering whether the balance of public interest in promoting independent research should outweigh the interests of patent holders (Cox, 1995). Courts could use patent overreach doctrine to reign in the level of protection afforded to patent owners in the area of GM crop technology. This would allow open and independent research of the effects of genetically modified foods on environment (Gray and Raybould, 1998; Rowe, 2010).

Because of this wide ranging opposition, a wide array of NGOs, more interested in pursuing an anticorporate agenda than a prodevelopment agenda, have worked to convince nations to ban or otherwise limit productivity enhancing GM crops. Consequently, in most cases, GM versions of crops simply don't exist. Even in the few cases where biotechnologically improved crops do exist, it is difficult or impossible for farmers to gain access, therefore, progress toward making GM crops with anticipated health benefits like golden rice, edible vaccines and healthy lipid biofortified seeds, and their myriad health benefits, has been set back significantly (Rosi et al., 2007; Hilbeck et al, 2011).

World Health Organization and several other regulatory agencies have been taking an active role in relation to GM crops specially GM foods. It is important and imperative that public health should benefit from the potential of biotechnology, like, substantial increase in the quantity and quality of the nutritional content of foods, decreased allergenicity and more efficient and/or sustainable food production (Paarlberg, 2010; Diels et al., 2011; ILSI, 2011). On the other hand, it is essential to examine the potential negative effects on human health of the consumption of food produced through genetic modification in order to protect public health. Modern technologies should be thoroughly evaluated if they are to constitute a true improvement in the way food is produced. Food and Agriculture Organization (FAO) is also aware of the underlined concerns about the potential risks posed by certain aspects of adopting newer biotechnology (FAO, 2002; EFSA, 2011). Caution and steps must be exercised in order to reduce the risks of transferring toxins from one life form to another, of creating new toxins or of transferring allergenic compounds from one species to another, which might result into unexpected allergic reactions among populations that happen to come under its direct or indirect contact (Freese and Schubert, 2004; Thudi et al., 2012).

Conclusion: GM foods have been researched, developed and marketed because of their perceived advantages, either to the producers or consumers and are meant to translate into a product of lower price, greater durability under stressful circumstances or the enhanced nutritional value or both. Initially, GM crop developers wanted their products to be accepted by producers and have concentrated on innovations that bring direct benefit to farmers (and the food industry generally). The GM crops currently on the market are mainly aimed at an increased level of crop protection through the introduction of resistance against plant diseases caused by insects or viruses or through increased tolerance towards herbicides. Pro GM technology Countries, where GM crops have been introduced and grown in fields, have not reported any significant health issues or environmental damage. Moreover, farmers there are using less pesticides or using less toxic ones, reducing harm to water supplies and workers health, and allowing the return of beneficial insects to the fields. Some of the concerns, that got immediate attention, related to horizontal gene flow and pest resistance have been addressed by new techniques of genetic engineering. However, the group of countries that oppose the technology are of the opinion that the lack of observed negative effects does not strictly mean that they cannot occur. Therefore, Scientists there, call for a cautious and rigorous case by case evaluation and assessment of each product or process prior to its release in order to address legitimate safety concerns falling under three parallel arms of investigations *i.e.* addressing toxicity, carcinogenicity, and multigenerational effects. What is needed are long term and multigenerational studies on GMOs to see if the changes found in short and medium term studies, which are suggestive of harmful health effects, develop into serious disease, premature death, or reproductive or developmental effects.

Further, Science cannot declare any technology completely risk free. GM crops can reduce some health and environmental risks associated with conventional agriculture, but will also introduce new challenges that must be assessed and addressed on regular basis. Society in the light of its scientific temperament shall have to decide when and where genetic engineering is safe enough. Nevertheless, genetic engineering, beyond doubt is the inevitable wave of the future and that we cannot afford to ignore this technology that has such enormous potential benefits. However, all must proceed with caution to avoid causing unintended harm to human health and the environment as a result of our enthusiasm for this powerful technology.

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