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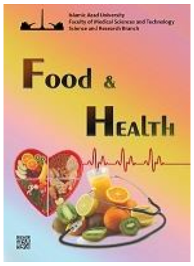

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Genetically modified foods: Pros and cons for human health

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Genetically modified foods (GM foods) have revolutionized the agricultural industry towards more proficient farming in every geographical region of the world. The major tasks of this GM food technology could be summarized in four points including increase in food products, more convenient food processing, disease prevention and treatment and avoiding of using pesticides through the generation of pest-resistant crops. Although the GM foods technology had great advantages for human health, there are some concerns regarding biodiversity induced by modified plants, which can indirectly affect human being, as well. Further studies are warranted to define precisely the status of this technology in ecosystem in which human is living.

1. Introduction

Genetically modified foods which are also known as GM foods or bioengineered foods are foods which are generated from organisms that their genomes have been undergone genetic manipulations and modifications to induce a novel trait in order to improve the quality or quantity of product. Although GM foods sometimes refer to the products from organisms along with genetic engineering, genetically modified organisms (GMOs) specifically stands for genetic engineering of animals to produce edible products with the novel or improved feature.

History of GM foods was officially begun since 1994 by the introduction of delayed-ripening tomato (known as Flavr Savr) which got received its approve in 1992 from food and drug administration (FDA) (1). However, the exact and real-time of the beginning of GM foods production may be returned to 10,500 to 10,100 BC when the farmers caused selective breeding through artificial selection and making crossing over between plants with genes encoding desired traits and characteristics (2). By the discovery of DNA structures and genes in later years, the possibility of direct engineering of various types of plants had been provided to reach the desired trait. GM foods industries had been worked on many different agricultural products with major aims of the followings:

1.1. Increasing food production

Enhancement of food productions was one of the most important reasons that led to the introduction of GM foods technology. The bitter fact behind this reason is the poor agricultural economy in developing and under developing countries due to having no access and enough money to buy pesticides to protect their products against pest and microbial contaminations (3). Moreover, with increasing in the world's population within the next half century, especially in developing countries, the demand for more productive and efficient food and agricultural industry will be more felt as well in spite of the decrease in water and early requirements supplies (4). Therefore, developing a strong agricultural industry not only can fulfill the future nutrition needs and prevent malnutritio but also can provide more and desire, and various types of unique products using less and inexpensive substrate and less plant treatment.

1.2. Food processing

Plants ripening rate is one of the most important factors in plant delivery and export and can indirectly affect the economy of a country. In this regard, the first delayed ripening plant which has been introduced by Calgene Company in 1994

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was tomato (Flavr Savr). It was made through the insertion of polygalacturonase inhibitor oligonucleotide into the genome of tomato to delay the ripening process. It is of note that polygalacturonase which is also known as pectin depolymerase degrades galacturonic acid within the pectin network and plays a critical role in smoothing and sweetening of fruits and plants as well as tomato (5). In reverse, accelerated ripening of some dairy products such as Cheddar cheese through over expression of enzymes involved in the ripening process has shown a remarkable improvement in the dairy industry and the economy (6). The same scenario has been introduced to double the growth rate of salmon fish through over expression of growth hormone which has to get its approval from FDA as the primary GMO (AquAdvantagea salmon) (7).

1.3. Using of GM foods as disease prophylaxis

One of the promising and interesting features of GM foods is genetic engineering in order to enhance the nutritional value of diet in the usual dietary sharing schedule. This is very important strategy in developing countries wherein in most of the times almost of the families eat an especial type of crop as well as rice or maize with specific and limited nutritional values which will definitely be associated with increased risk of malnutrition (3). This aim can be achieved through two general ways: the first one is known as biofortification with the main purpose of prevention of malnutrition and increasing the nutritional value of present foods. There are two major strategies in food fortification including direct addition of desired nutrients into the fertilizer and selective breeding of plant with or without directed mutated plants using selectable markers (8, 9). In the first strategy, successful fortification would consider the distribution of nutrient as well as minerals using the appropriate method and soil contents. As an instance, in the districts with Zn deficient soils, using of Zinc (Zn) fertilizers (such as $ZnSO_4$) which are highly mobile within the soil resulted in the production of Zn rich cereals and grains with the special trend in more Zn content in some specific plant genotypes (10). The same scenario is held for selenium and iodine as highly mobile mineral nutrients which have been introduced in selenium and iodine-poor soils of Finland and New Zealand (11, 12). The other example is using of Nitrogen Phosphorous and Potash Potassium (NPK) fertilizer in regions with poor soil of those nutrients which can effectively spread to the plant and enhance its growth (Fig. 1) (13). NPK fertilizer also can be used to increase the spread of other nutrients with low mobility such as iron (Fe) through acidification of soil in the case of NH_4 as an alternative to using of iron chelators as well as $FeSO_4$ sprays (13). The major drawback of this strategy is the need for the regular and expensive application of fertilizers, which may be also dangerous for the ecosystem. The other disadvantage is that it could be helpful for specific types and strains of grain and therefore cannot prevent all types of malnutrition. The second strategy is based on the selective breeding of plants with desired genetic composition to have more potent and rich products in next generations.

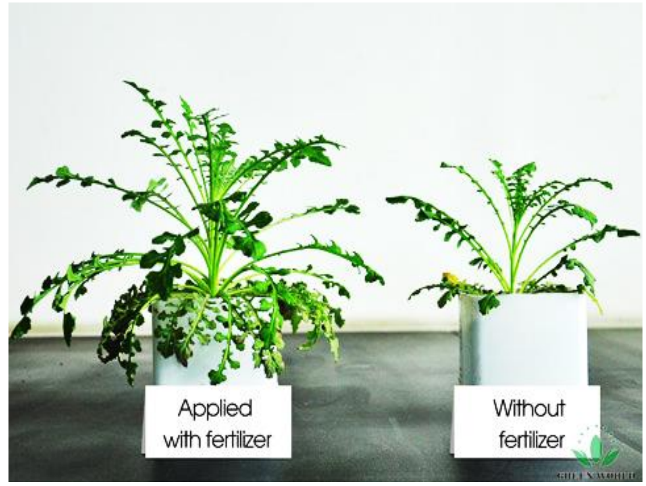

Fig. 1. Comparison of the growth of the same plants harvested with NPK (left) and without NPK (right).

This strategy is itself can be applied using two main policies which the first one is breeding with plants with dominant genotypes encoding higher amounts of nutrients and minerals. In this regard, a cooperative project was begun by Consultative Group on International Agricultural Research (CGIAR) to screen the plants (maize, wheat, cassava, rice, and bean) with genotypes encoding high amounts of Fe and Zn (14-16). The second policy is directed genetic manipulation of plant genome to overexpress the desired protein or other micro or macromolecules. Target proteins are almost traced element and metal binding proteins and transporter proteins that are abundant in the parts of the plant which are not usually edible (17, 18).

Genetic engineering of interest plant can be performed using different approaches including direct transfer of desired gene or direct manipulation of target plant genome using novel genetic engineering technologies as well as CRISPR-Cas9 system and indirect methods usually through making directed infection using bacterial cells containing plasmid to transfer and replicate the desired gene or genes in plant (19-21). One of the famous trace element binding proteins is leghemoglobin, which has a pivotal role in concentrating the iron reserve in the highly absorbable hem form. Overexpression of this protein in legumes and induced its transcription in other plants, as well as cereals, can have a dramatic effect on iron bioavailability in diets enriched with iron absorption inhibitors. However, the direction of targeted protein expression to the edible parts of plants seems to be unsuccessful in its initial attempts and requires further investigations (22). The other introduced strategies include insertion of phytase gene to break down the phytate as an inhibitory factor of trace element absorption (23), induced expression of vitamins with enhancing effects on metals and trace elements absorption as well as vitamin C or β-carotene (24) and overexpression of proteins containing amino acids which increase the bioavailability of trace elements as well as cysteine (25, 26).

1.4. Implication of GM foods in pharmacology and disease treatment

Another GM foods technology has relied on the production of an edible vaccine to not only increase the effect of it, but also alleviate the possible side effects of injectable vaccines. Plant-based vaccine technology can overcome the production and selling circle including the specific storage condition and costs which usually limit appropriate service in some regions and on biosafety concerns, as well (27). Interestingly, this strategy has been applied to another organism as well as fishes, which has provided effective, cost-benefit and easy to use vaccination (28). In fact, every part of the plant including fruit, stem, root and etc., can be used to enhance the immune system of the human host against various diseases especially infectious diseases by providing required proteins, vitamins, and other nutrients. This aim can be fulfilled by cloning the interest antigen-encoding gene into the desired part of the plant which will be edible and marketed. One of the amazing advantages of this strategy is that the introduced antigen will be enclosed in within the cellular wall of plant against enzymatic degradation and therefore leads to a higher level of immunization (29). The other interesting point of plant-based vaccination is that those vaccines will be introduced into the human body when the plant reaches the small intestine wherein antigens can be specifically absorbed and directed through special mechanisms through activation of both B and T cells responses (30, 31). However, some studies have demonstrated that edible vaccines may cause oral tolerance to introduce antigen due to the presentation of antigens to T cells by immature dendritic cells. In the production of a plant-derived vaccine against hepatitis B virus (HBV), this problem has been overcoming through using of carrier proteins as well as core protein (HBc Ag) as adjuvant or initiating the vaccination process by intramuscular administration to enhance the immune system excitation (32, 33). Among human vaccine, producing plant-derived malaria vaccine had been evaluated in many studies for more than one decade. Although the frequency and mortality rate of malaria has been remarkably decreased, demand for cost-effective and easy using vaccine with a minimum rate of side effects and enough immune response in oral administration is still strongly felt (34). The other amazing examples of plant-derived vaccine were potato and corn which were genetically engineered to express enterotoxigenic *E. coli* (ETEC) toxin called LT-B which is standing for B subunit of it. The advantage of this type of vaccine was described to excite the immune response against glycolipids of the plant cell membrane bound with LT-B without inducing diarrhea and thereby immunize the patient against *E. coli* contamination in a safe, easy and relatively cheap manner (35). The same procedure has been performed on norovirus, influenza and hepatitis B and even human immunodeficiency virus (HIV) through expression of immunogenic capsid protein within the virus-like particles (VLP) which is not infective in transgenic tobacco leaves, potato tubers, lettuce, tobacco, tomato, carrot, rice, maize, and Arabidopsis (36-42). There are other plant-based vaccines which are some of them are in the final phases of clinical trials including H5 pandemic influenza, seasonal influenza, Ebola Virus, Hepatitis C virus (HCV) and human papillomavirus (HPV) (43-47). Anthrax which is an infection caused by Bacillus anthracis and frequently involves skin and intestine has been shown to be effectively preventive in mice and rabbit by genetic engineering of Nicotiana benthamiana as vaccine (48). Another medicine based application of GM foods is improvement in enzyme replacement therapy (ERT) which had been successful in getting food and drug administration (FDA) approval. One of the best examples is ERT of Gaucher's disease in which the patients have hereditary deficiency of the enzyme glucocerebrosidase actively involved in the metabolism of glucocerebroside. In this regard, the primary FDA approval has been devoted to the novel Plant molecular farming (PMF) approach marketed by Protalix and used to induce the expression of the same enzyme, recombinant taliglucerase alpha, in transgenic carrot cells (49, 50). The second enzyme deficiency disease is Fabry disease, which is as a result of defective metabolism of sphingolipids (α-Galactosidase-A deficiency) and their accumulation in the nervous system and other parts of the body. PRX-102 is a novel enzyme with the same structure and function of α-Galactosidase, an enzyme which has been expressed and marketed by from Protalix with significant stability compared to commercial enzyme through genetic engineering of tobacco, and *Nicotiana benthamiana* Leaves are passing through the phase I and II of clinical trials (45, 51). Plant based medicines have seized the greater attention to be used in cancer immunotherapy in other ways than dietary administration. Plant aided immunotherapy has been fulfilled through using almost of plant viruses as well as potexvirus PVX as a carrier of antigen targeting tumor cells within the structure of drug conjugates to efficiently excite immune response against tumor cells (52, 53).

1.5. Resistance to insect and infectious agents

Almost all of the plants are susceptible to be infected or damaged with different types of insects and plant-specific infections such as fungi, nematodes, viruses, and bacteria. Those infections not only threaten the agricultural economy of a country, but also sometimes may have dangerous side effects on human health. In this regard, making foods with higher stability and tolerance against contamination including overexpression or inducing resistance of herbicide target proteins and enhancing the expression of proteins responsible for the degradation of substantial herbicide factors, had a dramatic improvement in cultivar plants especially crops. The initial trials have been performed by Calgene company in 1987 by introducing tobacco with tolerance to herbicides containing enzymes as well as glyphosate, bromoxynil, and sulfonylurea (54, 55). The technology of herbicide-resistant (HR) crops has been developed since 1996 to efficiently control the weeds. Weeds usually compete with plants using water, nutrients and especially space of growth and thereby constrain the production of their interest targets.

Recently, Iquebal et al. (56) have primarily studied the gene expression profile of chickpea to identify the important genes associated with tolerance to herbicide Imazethapyr. Chickpea belongs to legume crops which is a comparable source of protein relative to animal products. Shoba et al. (57) were successful in making directed mutagenesis in rice called HTM-N22 which was tolerant to Imazethapyr, as well. The most recent approach in developing pest-resistant plants is inhibitory RNA (iRNA) mediated suppression of pests as well as Aphids (Aphididae) (58). The mechanism of action of all the iRNAs is suppression of target RNA translation through forming RNA induced silencing complex (RISC). This is a natural defense against viral infection in most of the Eukaryotes as well as plants which can be directed against any other pest or parasite by designing the nucleotide sequence of miRNA complementary to the major target gene encoding protein of parasite (59). There are many reports conferring using many different approaches in producing plants resistant to insects through cloning of gene encoding of toxin derived from different bacterial cells. As an instance, transgenic rice encoding *Bacillus thuringiensis* (Bt) toxin has shown to be successful in protecting them against the attack of spiders with no side effect on spiders population (60). Another example is insect resistant maize called TC1507 which has been transfected with modified Cry1F and PAT genes and has been approved to be cultivated in the US since 2001(61).

2. What is behind GM foods consumption?

GM foods and GMO had a major improvement in agricultural technologies including overproduction of plants in less time, no further need to use pesticides with carcinogenic effects, the possibility of growing plants in every geographical region with every soil composition, help to save fossil fuels and less CO_2 emission. The mentioned major agricultural and environmental advantages of GM foods technology have indirectly improved human health as well as edible vaccines, which can remarkably influence the disease incidence and their prevention, especially in developing countries. Despite those benefits and advantages, there are some other concerns regarding taking GM foods, which have been noted in different studies. Those concerns can be discussed in two ways including the effect on the first environment and ecosystem and the second with more importance in human health. One of the main studied aspects of ecosystem affected by GM foods is changing in the food web of some animals as well as arthropod especially in the long-term assay (62, 63). As an instance, some studies have revealed that Bt maize has raised the frequency of other nontarget organisms which can indirectly affect the arthropod mortality rate (64).

The other aspect which can be influenced by GM foods is gene flow through breeding between GM and non-GM plants which is itself can be affected by different biotechnological and environmental factors (65). In this case, gene flow not only results in unwanted contamination of non-GM plants but also the generated hybrid plants hybridized usually are less fit compared to wild ones (66). Although it seems that natural selection is the final determinant of detrimental or favorite allele's frequency within agricultural land, generation of transient invasive or abnormal plants may have crucial impacts on the regional economy. The chemistry of soil including PH, phosphorous, potassium and organic matters has been shown to be changed in area cultivated with GM plants versus non-GM plants (67). Regarding the effects of GM foods with the aim of prevention or treatment of the diseases on human health, we should keep in our mind that every drug with FDA approve has its own adverse effect and uncontrolled consumption of even natural foods and plants has definitely side effects which may threaten health status of peoples. However, despite many investigations performed in animal studies, there is no report indicating no histopathologic or clinical side effects (68). However, every genetic modification has a chance to be associated with unintended helpful or harmful mutations within the target genome including deletion, insertion, and translocations. Based on Codex Alimentarius claims, these induced genetic alterations can also be detected in normal plants breeding rather than GM foods. Among various Food and Drug organizations, Food Standards Australia New Zealand (FSANZ) has restricted using of GM foods following further assessments on human and animal studies (68).

3. Conclusion

Taken together, GM foods had great effects on human health and agriculture industry improvements. Despite some controversial reports on possible side effects of GM foods in animal studies and on the biodiversity of plants, review of the present studies is indicating that these impacts are mostly transient and like other genetic changes would be lost or existed by natural selection. However, further large-scale and long-term analysis of both animal and human are warranted to define clearly the status of GM foods in nature's food chains. This study looked at the possibility of using polymeric nanoparticles containing alpha-tocopherol to produce biologic preservatives to improve health and focus on consumer health. The optimization of nanoparticles characteristics and the study of morphological properties, size, zeta potential, bond properties, and their calorimetry were carried out. The smallest size of nanoparticles was related to the sample with the lowest alpha-tocopherol density, which was increased by increasing the percentage of alpha-tocopherol percentage. Despite the decrease in the accumulation rate, due to the imbalance in electrostatic balance and surface accumulation of alpha-tocopherol.

Conflict of interest

The authors declare no conflicts of interest.

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