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Review

Myths and Realities about Genetically Modified Food: A Risk-Benefit Analysis

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Abstract: The development and consumption of genetically modified (GM) crops are surrounded by controversy. According to proponents, only molecular biology approaches and genetic engineering tools are realistic food shortage solutions for the world's ever-growing population. The main purpose of this study is to review the impact of GM products on human, animal, and environmental health. People still reject GM crops not only because of safety concerns, but also for moral reasons. Toxicity, allergies, and possible horizontal gene transfer (HGT) to the environment or to other species have been associated with the marketing of GM products. Moreover, the scarce data available about the long-term implications of using GM crops is another opponent concern. Nevertheless, science has evidenced no harm from GM crops use to date but has, instead, reported several benefits that result from their commercialization, such as economic, environmental, and health benefits for the general public. Legislation and policies about GM product labeling standards are being discussed. To overcome emerging food security challenges, considering quality scientific information is essential rather than leaving the issue and merely moving toward moral discussion. Hence, a risk–benefit analysis is necessary.

Keywords: GM crops; genetic engineering; food security; labeling; legal framework

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1. Introduction

One of the marked public health achievements in modern history has been the acceleration of global food production in recent decades. The Green Revolution of the 1960s led key staple grain crops yields to significantly rise to cover the calorie demands of a growing population worldwide [1,2]. Technological innovations partly motivated this achievement, particularly the introduction of new synthetic chemical fertilizer and pesticide types in the 1940s, the development of higher-yielding grain varieties, agricultural labor being mechanized, and high-yield practices being adopted, including monocropping [3]. Unfortunately, malnutrition is still a leading risk factor for health consequences and death globally. Recent research reveals that 2 billion people are deficient in one micronutrient or more, almost 820 million people go hungry, and approximately 26.4% of the world's population is affected by moderate and severe food insecurity [4]. Finally, the most recent available analysis reports that undernourishment is associated with 3 million child deaths a year or half of all child deaths in the world [5].

As we look forward, we face one of the most formidable challenges of the 21st century: global food demand is expected to steeply continue to rise. A United Nations (UN) report states that the world population is expected to reach 9.8 billion by 2050 [6]. On the one hand,

this increase poses colossal food production challenges because crop yield rates do not feed the world's population [7,8]. On the other hand, economic expansion, globalization, and population growth have brought about structural shifts in consumption patterns worldwide. Surprisingly, meat demand has grown the most in the world, and the cattle industry has been identified to emit the most greenhouse gases. This rising demand has significantly impacted carbon emissions and land use [9]. Moreover, climate change and less cultivable land have resulted in an additional challenge to cover growing food demand [10]. Climate change is associated with rising temperatures and more extreme weather events, such as hurricanes, floods, droughts, and rainstorms. Apart from altered environmental conditions under which food production operates, there are fewer pollinating insects, increasing water scarcity, and alterations to relations linking pests, crops, weeds, and pathogens [1]. The analysis revealed that these situations could be daunting if no action is taken [10]. Here, we contemplate the potential of genetically modified (GM) crops to enhance sustainable food production [11].

The concept of "genetically modified organisms" (GMOs) refers to those organisms whose genome has been altered by inserting a gene from another organism, removing a gene, or changing a gene's function to generate a desirable trait. These genes can come from the same species or a different one. Thus, species boundaries may be crossed to produce novel crops [12]. Depending on the final destination, GMOs can be classified as GM food when the direct consumers are humans and as GM feed when products are intended only for animals. It has been estimated that 70–90% of all GM crops are employed as animal feed [13]. The market share of GM products has grown since the first generations of GM crops were commercialized in the 1990s. The four leading biotech crops are maize, cotton, soybeans, and canola. Based on the global cultivated area for individual crops, 32% of maize, 80% of cotton, 77% of soybeans, and 30% of canola were biotech crops in 2017 (Figure 1). Herbicide tolerance has been a consistent dominant trait which, in 2018, covered 46% of the global area (a 1% drop compared to 2017) [14]. Today, the commercial use of GM crops also extends to other foods, such as sugar beet, papaya, eggplant *Solanum melongena*, potatoes, and apples [8].

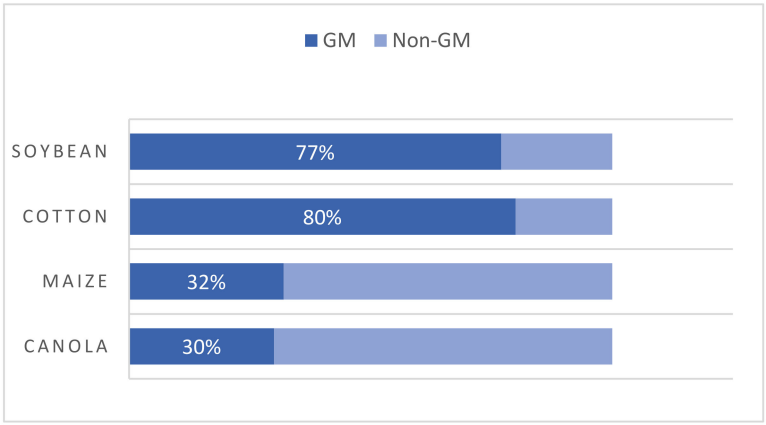

Figure 1. Percentages of the main biotech crops in 2017. Adapted from [14].

In recent decades, technological molecular biology and genetic engineering (GE) advancements have enabled crops to be developed with improved traits, such as herbicide tolerance, good insect resistance, or better yields [15]. Moreover, interest in developing GM crops with improved nutritional properties is growing, such as higher levels of essential microelements, healthier crops by altering their fatty acids profile, or plants with delayed ripening [16]. Ever since the first GM food was introduced, the debate about the risks of releasing GM crops has been substantial. Lawmakers, scientists, and consumers have been divided on the subject of using GMOs to produce food and feed. Supporters believe that new crop enhancement advances could be a promising solution to ensure food security and cover increasing food demands [17]. This review presents a risk–benefit analysis of

GM food consumption to highlight how biotechnology can help to improve human health and cushion environmental impacts.

2. Legislative Framework of Genetically Modified (GM) Crops

Both GM crops and their products must be rigorously evaluated before being commercially released. The legal framework that regulates GM food and feed attempts to ensure high protection levels for human and animal health and also for the environment [8]. Worldwide, the authorities responsible for evaluating GM products have adopted specific strategies based on the amount of experience and scientific knowledge acquired in the past few decades to assess their safety [18]. These principles were first submitted in 1993 by the Organization for Economic Co-operation and Development (OECD) and were further detailed by an international body jointly established by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) of the United Nations [19,20].

In 1963, the FAO and the WHO created the Codex Alimentarius Commission. The Codex develops international food standards, guidelines, and codes of practice to protect the health of consumers and to ensure fair practices in food trade. Moreover, it promotes the coordination of all food standards work undertaken by international organizations [21]. In 1999, the Codex established the Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology (Figure 2). This group is responsible for developing and setting up guidelines, standards, or recommendations for foods that derive from applying modern biotechnology. The Task Force published three documents in 2003 that were adopted by Codex: Principles for the Risk Analysis of Foods Derived from Modern Biotechnology; Guideline for Safety Assessment of Foods Derived from Recombinant-DNA Plants; Guideline for Safety Assessment of Foods Derived from Recombinant-DNA Microbes [19]. The first document is a framework for performing risk analyses on either whole food derived from using biotechnology or the components of those foods. It discusses risk assessment, risk management, and risk communication. The Plant Guideline contains further details about the principles for risk analyses of foods derived from modern biotechnology. Specifically, paragraph 18 describes the framework for making such a safety assessment of food derived from a recombinant-DNA plant. This safety assessment framework follows a stepwise process to address relevant factors [18,19] (Figure 2).

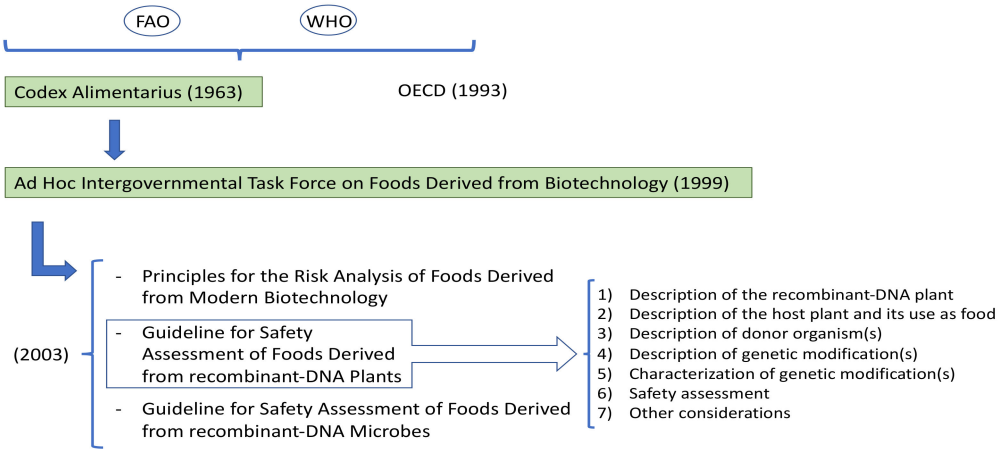

Figure 2. Development of standards and recommendations for products resulting from biotechnology.

Labeling GMOs is also essential for helping consumers to make informed decisions. Consumers care about certain details, such as source, if food is processed, and if it contains additives [22]. GMOs are surrounded by plenty of controversies. Since the first GM products were commercially released, the debate about the real perceived risks of using GMOs has been underway. While dispute rages on, the public's GM crop concerns have prompted governments to step in and adopt legislation that insists on GM products being labeled [17]. Notwithstanding, no agreement has been reached by government agencies about manda-

tory labeling, which renders the strategy ineffective and also makes transportation and trade extremely difficult [17,23].

The dispute over GMO labeling is structured on how much information consumers should receive and if this information provides enough knowledge about the contents to help consumers make better decisions. A difference exists between voluntary and mandatory GMO labeling. Voluntary labeling informs consumers that products do not contain bioengineered substances. Mandatory labeling goes much further because it expects all food products that contain GMOs to include warning labels [17]. Both these labeling schemes have their pros and cons. Consumers have the right to know what their food contains, and labeling must help them make purchasing decisions. However, as consumer knowledge about new technology such as GE is limited, they cannot often establish whether GM products spell danger or how to measure any given risk against potential benefits. Hence, individuals rely on those people they perceive as being trustworthy experts to reach informed conclusions, which they might use to form their own views. Consequently, trust is critical in layperson evaluations of GM foods [24].

The first labeling legislation on GM foods was framed by the European Union (EU) in 1997. Later, more modifications were made to legislation on GMO derivatives [25]. In 2007, the Codex Alimentarius Commission made an attempt to produce labeling guidelines for biotech products, but it was prevented because no consensus was reached by different countries [26]. Nonetheless, an increasing number of countries have been involved in labeling with distinct regulatory characteristics [17]. At least 64 countries worldwide, such as the EU countries, China and Australia, expect some form of GMO labeling [24]. Policies and the extent to which they are adopted differ from one country to the next. The Codex Committee has addressed the costs incurred to implement and enforce labeling, as well as potential advantages. Test requirements, agricultural production traceability, processing and distribution, document verification, analytical method feasibility and detection limits, and consumer education are only some of the main concerns being addressed. It would appear unlikely that a worldwide agreement will be reached in the near future because the USA strongly opposes labeling. The US GM labeling position is based on the "substantial equivalence" (SE) premise [17]. This concept first appeared in 1993 and embodies the notion that if a novel food has the same composition and features as conventional food, then it must be taken as safe as conventional food [20]. Proponents of the SE principle state that requiring labeling is not necessary because customers are more concerned about health and safety, functionality, and food usage than about manufacturing processes. Mandatory GMO labeling gives an impression, and even serves as a warning, that these foods differ or are less safe than their non-GM counterparts. The EU takes a "precautionary stance". As the perceived or true risk of GMOs in long-term exposure remains unknown, labeling is vital for traceability considerations, along with consumer "right to know" legislation. According to the EU, it is no easy task to contemplate and measure the effects of these foods because the population has not been exposed for very long. Lack of evidence does not rule out the time-lag potential between exposure to health/environmental dangers and their consequences [17].

The EU Regulatory Framework of GMOs

The EU has set up a legal framework to disseminate GMOs on markets to ensure high protection levels for human/animal health and the environment. The aim of this regulatory framework is to confer in the authorization process a high degree of transparency. It is based on three basic principles: pre-market authorization based on a prior risk assessment; traceability; labeling [27]. GM foods and feeds in the EU can be approved provided that they successfully pass rigorous safety assessments [28]. The procedures to assess and authorize GM foods and feeds appear in the following documents: (1) Directive 2001/18/EC, which regulates the authorization of deliberate releases and placing GMOs on the market; (2) EC Regulation No. 1829/ 2003, which provides a specific authorization procedure of GM foods and feeds [29,30]. These documents provide rules for GMO safety assessments by

regulating GM food and feed production, GMO imports, and the release of GMOs into the environment [18].

A GMO authorization is granted as long as no adverse health or environmental effect is identified. In the EU, the European Food Safety Authority (EFSA) plays the main role in risk assessments [27]. The EFSA's role is to assess the safety of new GMOs and to provide scientific advice before Europe's risk managers make decisions (the European Commission and EU Member States). EFSA assessments are made according to applicants' scientific dossiers and any other relevant scientific data. They bear in mind these aspects: (1) molecular characterization; (2) comparative analysis between the GM plant and its conventional counterpart; (3) evaluation of potential toxicity and allergenicity; (4) evaluation of potential environmental impacts. According to EU legislation, all Member States can decide about cultivating GM crops in their territories. Once a GMO is authorized, it usually receives a 10-year EU market license. Later, it must be re-assessed by the EFSA before any more re-authorization decisions are made [28].

Labeling and traceability rules guarantee operators and consumers access to crucial GMO information [27]. In line with EC Regulation No. 1829/2003 on GM food and feed and No. 1830/2003 on the traceability and labeling of GMOs, products consisting of or containing authorized GMOs or produced from GMOs must be clearly labeled as such. These requirements do not apply to foods containing < 0.9% authorized GM material as long as the GM material is technically or adventitiously unavoidable [27,31]. The EU framework sets a traceability and labeling threshold for approved GMOs, and a "zero tolerance" policy exists for unapproved GMOs. What they mean is that unapproved GMOs in the EU cannot be sold [31]. Several EU Member States have enacted their own national regulations that permit the voluntary labeling of "GMO-free food or feed" or "food that originates from animals not fed GM feed" [32].

The EU GMO regulation includes effective enforcement provisions. Those applicants who wish to place GMOs on the EU market must set up and submit an acceptable detection method, positive and negative control samples, and certified reference material. These methods form part of the national authorities' control and inspection systems to make sure that any GMOs placed on the market have been duly approved and labeled according to legislation [27].

3. Myths and Realities of GM Crops: Risk Assessment

Humans have been altering plant and animal genomes for thousands of years [33]. Since ancient times, selective breeding, also called artificial selection, has been a routine method in agriculture [34]. For instance, humans have driven maize evolution from a plant with many branches and small cobs to a plant with fewer larger stalks and larger kernels, which result from the selective seed selection of plants with highly desirable traits [35]. Something similar has taken place with tomatoes, which are the product of applying careful genetic selection to alter their size, shape, seeds, and taste (Figure 3) [36]. Although the process of creating new traits takes time because it requires spontaneous genetic mutations, the development of GE tools has accelerated the production of GMOs [34].

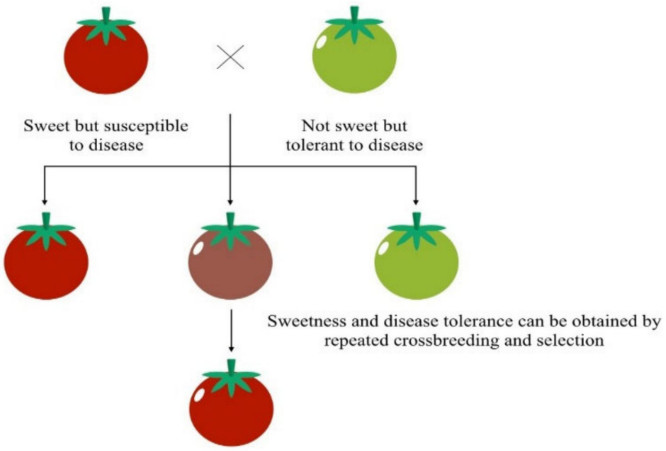

Figure 3. Selective tomato breeding. Icons made by Freepik and Smashicons from www.flaticon.com (accessed on 1 December 2021). Adapted from [37].

The first transgenic plant was created in 1983: a tobacco plant that resists antibiotics [33]. Nevertheless, the first GM food was not marketed in the USA until 1994: the Flavr SavrTM late-ripening tomato. Although the Flavr SavrTM tomato study was a scientific success, public opinion forged its commercial failure [38]. One reason for its commercial failure was that GM foods inspired moral debate that was closely tied to views on what is considered "unnatural". Religion is generally associated with opposing GE, and some people believe that it is like "playing God" [34,39]. Nonetheless, there is evidence that gene transfer between species is not as unnatural as we think. For instance, *Elysia chlorotica* is a marine gastropod mollusk that has integrated a gene from an alga into its genome, which confers on it a photosynthetic capability [40].

Anti-GMO activists argue that GM crops occupy much space and are related to intense monoculture systems. Despite monoculture agriculture offering many advantages, it is still a very controversial issue in modern agriculture. Monocropping implies lots of disadvantages, including biological diversity loss. As biodiversity is lacking, crops are more susceptible to pests, and these threats spread more quickly. Consequently, farmers apply more herbicides and pesticides to safeguard crops. These pollutants normally sink into the earth and pollute both soil and groundwater. As monoculture farming exhausts soil by depriving it of biodiversity, farmers will wish to artificially enhance the fertility of their affected fields and apply chemical fertilizers. Artificial nutrients severely impact the natural soil composition and, thus, have a destructive effect on the ecosystem as a whole. Applying herbicides, pesticides, and other chemicals strongly impacts bees and other pollinators (Earth Observing System). Yet monoculture is essential for feeding the world population and has extended nearly 5-fold since 1900. From the agronomic viewpoint, it is the monoculture size (temporal and geographical) that makes it beneficial or harmful. Farmers face the challenge of implementing long-term crop management strategies, crop rotation, and farm management to protect soil health and biodiversity. In relation to GM crops, and based on the history of such practice, they have nothing to do with monocropping's origins. Farmers have performed monoculture farming worldwide long before GM seeds appeared on the market. Employing GM crops enhances yields and reduces deforestation and other damaging activities carried out to generate farmland. Nowadays, more and diverse fruit and vegetables are available than ever before. GM seed varieties created specially to include genes from other plants and bacteria widened the genetic diversity of large commodity crops in the 1990s [41] (Genetic Literacy Project).

Recently, a survey revealed that consumer GM food views have barely changed since they were introduced in the mid-1990s. Europeans perceive that GMOs are unsafe, and they believe that they can harm not only consumers but also the environment [42]. According to the 2005 Pew Initiative, 50% of Americans are unaware of GM foods and oppose them being introduced into the food system [43]. However, the acceptance of GM foods appears

to depend on their development and intended use. For example, modifications made to increase nutritional values are more widely accepted than those made to simply increase crop yields. On the other hand, based on the sort of genetic alteration conducted, "cisgenic" changes are preferred over "transgenic" modifications [44] (Figure 4). The conclusion is that "the more distant the relation between the organisms, the less accepted the modification seems to be" [45].

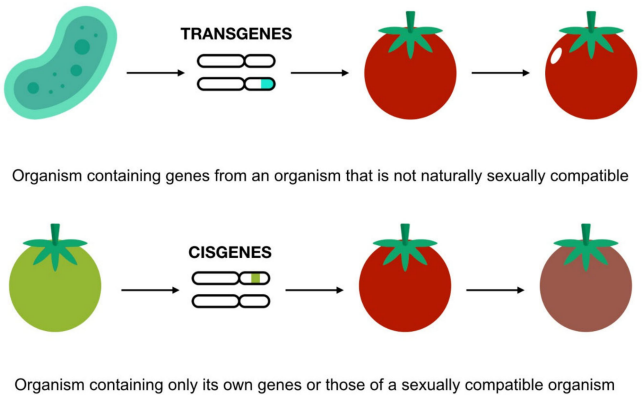

Figure 4. Cisgenic and transgenic modification. Icons made by Freepik and Smashicons from www.flaticon.com (accessed on 1 December 2021). Adapted from [46].

Many prevalent GE myths exist and cover wide-ranging themes, from health and safety to other environmental safety areas. Allergies, toxicity, possible horizontal gene transfer (HGT) to the environment or other species, and several anomalies such as metabolic disturbance, tumor genesis, or infertility have all been related to the consumption of GM crops. Overall, the considerable scientific consensus holds, insofar as currently marketed GM food does not pose a higher risk than traditional food [8,33,47]. The authors offer a risk–benefit analysis based on scientific evidence and debunk myths that interest groups have spread.

3.1. Environmental Safety Studies

The main purpose of environmental risk assessments (ERA) is to determine whether a new GM crop variety has direct effects on the natural environment. These risk assessments aim to establish the effects that GE technology crops have on biodiversity in plant and animal communities, the diversity of crop species, and the potential effects on ecosystems and landscapes such as changes in soil and water qualities [8,48]. The international regulatory instrument known as the Cartagena Protocol on Biosafety (CPB) intends to protect biodiversity from the possible threats posed by GM crops. This protocol states that the precautionary principle should be applied to safeguard the environment. Nevertheless, no uniform ERA GM crop procedures have been devised, and every country's laws govern this situation [8]. Today, the ideal methodology followed to analyze the environmental risks posed by GM crops is the case-by-case assessment. The familiarity concept has also spread internationally in the GMO environmental safety context: becoming familiar implies acquiring enough information to facilitate risk and safety assessments. As familiarity is based on comprehending the ecosystem and its interactions with any introduced organisms, risk and safety assessments in one region might not be applicable to another [49].

Evidence for relating GM crops to adverse agronomic or environmental problems is scarce. Regarding agronomic aspects, the introduction of GM crops has not resulted in increased on-farm crop yields, except when insect-pest pressure is high. However, given the varying adoption rates of GM crops taken by farmers, as well as differences in land quality and financial resources, it has sometimes not been easy to determine the qualitative contribution of GM crop traits. Hence, it is important to enhance experimental approaches that disentangle the effects of GM traits from other factors [48]. The main concern of ERA is the gene flow (GF) of the transgene(s) to wild relatives [50]. The GF is the result of moving

gametes or individuals from a specific population to another, not only between populations of the same species but also between closely related species. This occurrence could lead to a marked change in the receiving population's allele frequency [8,51]. This mobility may take place in natural plant populations by vegetative propagules, seeds, or pollen, and its relevance varies per plant species [52]. To gain insight into the rates and importance of hybridization, general ways of quantifying the GF utilize foreign herbicide and antibiotic resistance genes. Morphological and molecular markers are also needed to quickly help to identify or to identify/confirm hybrids [8].

The potential risk of the GF to produce cross-pollination between GM crops and wild species has been discussed. While producing commercial GM crops, a pollen-mediated GF has been reported in maize, cotton, soybean, and other species. The term "co-existence" was introduced to limit any undesired GF and to allow GM and non-GM crops to exist with mutual tolerance [53]. According to the 2003 Commission Recommendation definition, "co-existence refers to the ability of farmers to make a practical choice between conventional, organic, and GM-crop production, in compliance with the legal obligations for labeling and/or purity standards" [54]. This concept refers to consumers' right to choose among conventional, organic, and GM crops [53]. To make this right of choice possible, it is necessary not only to isolate the three supply chains but also to provide each one with the economic viability to survive. Co-existence can be defined as the minimum distance between GM and non-GM crop fields of the same species that should prevent the cross-pollination rate from reaching threshold levels [55]. Many factors influence the determination of appropriate isolation distances, such as local wind conditions or flowering synchrony between donor and receiver fields. Table 1 shows the minimum distances required for the four major GM crops (maize, canola, soybean, cotton) to keep cross-fertilization ratios below legal tolerance thresholds. For instance, research studies have shown that the required isolation distance to maintain cross-fertilization levels below 1% in maize crops is 20 m [8]. Isolation is only possible with a functioning traceability and labeling system [56] from farms to final consumers.

Table 1. Isolation distances required for the four major GM crops [8].

Crop	Isolation Distance	Cross-Fertilization Level	References
Maize	50 m 20 m	<0.5% <1%	[57] [58]
Canola	30 m 33–200 m	<0.03% <0.015%	[59] [60]
Soybean	5 m >10 m	0.9% 0.1%	[61]
Cotton	10 m >9 m	<0.9% <0.1%	[62] [63]
Alfalfa	50 m 20 m	1.39% 0.08%	[64]

3.2. Horizontal Gene Transfer (HGT)

Fred Griffith described the mechanism of transferring genetic material from heat-killed virulent *S. pneumoniae* to an avirulent type of the bacterium, which he referred to as transformation. Conjugation, transduction, and other types of nonreproductive gene transfer between organisms were later identified and documented [65]. HGT refers to the movement of genetic material to a living cell or organism across boundaries between species with no reproduction or human intervention [8,66]. HGT can occur between not only closely related but also distantly related organisms, such as viruses and animals or plants and bacteria. It is a process that occurs in two steps: the first consists of donor genetic material passing across the cell membrane(s) of the recipient cell, including other envelope

structures such as a cell wall or nuclear membrane; the second involves the incorporation of donor genetic material into the genome of the recipient organism so that the new gene can be perpetuated through offspring. If the receiving organism is multicellular, the transfer should be to germ cells, which are less present and less accessible than somatic cells [66]. This phenomenon has helped with the emergence of greater virulence in bacteria, eukaryotes, and viruses and in the rapid spread of antibiotic resistance among pathogenic bacteria [66–68].

Some concerns have been voiced in recent years about consuming GM food as they can produce HGT and compromise consumer health [69]. However, it is noteworthy that HGT is not an adverse effect of GM food consumption but an event that may, or may not, lead to harm. Hence, the need to make risk assessments that include both the severity and likelihood of negative consequences is essential [66]. A sequence of chain events establishes the probability of HGT posing a consumer health risk: an encounter between the recipient organism and the genetic material from the donor organism; donor genetic material entering the cell or the nucleus; integration of donor DNA or RNA into the recipient organism's genome; the expression of a novel trait in the recipient organism; the persistence of this trait and its passage to offspring [70]. For all these reasons, even if the frequency of HGT is high, a near-zero probability of any of the other processes reduces the overall possibility of injury to a near-zero level. If genetic material from GM plants is transferred to animals, the most feasible route is for DNA to be incorporated via the gastrointestinal route [71]. DNA segments can survive intestinal juices, which means only a slight possibility of recombinant DNA being incorporated into the human or animal genome of digestive organs. However, most studies conclude that such an HGT risk is insignificant [72]. The possibility of recombinant DNA inheritance in the following generation is also insignificant because the probability of DNA reaching germ cells and joining the genome with a suitable promoter is even lower [66]. Many pathogenic and opportunistic bacteria form part of the intestinal microbiota. Gene transfer to bacteria is an event that more easily occurs. However, these genes are often abundant in the environment and are equally transferable by conjugation and transduction [8,66]. Although this is not a probable event, both the WHO and FAO have encouraged using gene transfer technology that does not involve antibiotic resistance [72]. Based on current scientific evidence, HGT between GM plants and other organisms poses non-significant risks for human health and environmental safety because these events are rare [8,58].

3.3. Allergenicity Studies

In the USA, concerns have been voiced about the possibility of allergic reactions as a result of consuming GM foods. Consequently, several GM crops are unapproved for human consumption by the US authorities [8]. For example, a 2S albumin gene from Brazil nut has been inserted into a soybean cultivar for nutritional purposes. However, the GM product has been demonstrated to pose a risk of human allergic reactions, particularly in people with Brazil nut allergy [8,73]. Concerns about the Cry9C protein, a type of insect pest-resistance protein, have been voiced, given its greater heat stability and a possible longer digesting time. Yet, no direct association exists between allergic reactions and consuming GM food [8,74].

The WHO declared that it is not possible to generalize about the safety of GM crops, and, instead, each case must be individually assessed [72]. Marketed GM crops have previously passed risk assessments, including allergenicity tests; no case reports exist about the immunotoxic effects or allergic reactions that result from consuming them. In humans, no technique has been established to predict allergic responses to non-endogenous proteins. According to the EFSA, animal models should be employed to evaluate the sensitizing potential of new proteins on a case-by-case basis [75]. Rodent models are more frequently utilized for immunotoxicity and allergenicity studies [76]. Whether these models accurately describe the allergenicity of proteins in humans or cattle is a matter of debate. Thus, developing validated standardized animal models to assess allergenicity is vital [8]. Apart

from animal models, in vitro digestibility tests, amino acid sequence homology, and serum screening are currently the most popular methods to determine allergenicity [77] (Table 2).

Table 2. Some of the most popular methods for determining allergenicity.

Method	Basis
Amino acid sequence homology	A bioinformatic approach run to establish if a new protein is closely related to a known allergen. However, these approaches cannot predict if a new protein will become an allergy, so other methods might be required [78,79].
In vitro digestibility tests	It provides information about a new protein's susceptibility to digestion. The in vitro pepsin resistance assay is the most widespread protein digestion test [78].
Serum screening and immunoassays	Methods to assess endogenous allergens that employ human sera from people with relevant allergies. Despite these tests being the present gold standard for the in vitro detection and characterization of allergenic proteins, their utility in GM feed safety assessments is limited [8,80].

3.4. Toxicological Studies

As they have been designed to identify newly expressed chemicals, toxicological and allergenicity studies can be simultaneously carried out [8]. Allergenic reactions can induce severe symptoms, but only in some people. Toxicity is predictable and repeatable as it affects the vast majority of people with only modest susceptibility variances [81]. Toxicological works are conducted to detect unintended hazardous effects [8]. Toxicity can occur not only when the transgene encodes a toxin but also when it poses an unexpected toxic effect, e.g., gene repression or promotes toxin overexpression [82]. All toxicity evaluations should be done for GM crops on a case-by-case basis and must bear in mind the toxicological profile of newly introduced chemicals [83]. Animal studies are often conducted to establish a specific substance's toxicity. By way of example, an in vivo animal study has been conducted to evaluate the safety of transgenic rice EH rich in b-carotene. Two experimental groups of rats were established to measure distinct parameters: anatomy, growth, or serum chemistry indicators. The obtained results showed that GM rice was as nutritious as non-GM rice, and unintended effects were lacking [84].

New methodologies such as high-throughput "-omics" profiling techniques, which include transcriptomics, metabolomics, and proteomics, have been reported for identifying toxicants in GM crops [8,85]. For example, the omics approaches in the GM field have been employed in several research works into fungi and their secondary metabolites. Mycotoxins are the substances generated by crop-related fungi, and they pose a serious risk. GM maize resistant to insect pests contained a lower mycotoxin concentration than non-GM maize. As both fungus spore migration and colonization can be assisted by insect harm, it has been postulated that the observed drop in mycotoxins could be attributed to pest reduction in GM maize [8].

Glyphosate-resistant GM plants are one of the most controversial available biotech crops. The long-term toxicity of both Roundup herbicide and glyphosate-tolerant GM maize NK603 was the basis of contentious research published in 2012. The G-TwYST research collaboration assessed glyphosate-resistant genetically modified maize NK603 for toxicity and carcinogenicity. It was financed by the European Commission. This research reported no negative consequences from feeding the NK603 maize grown with or without Roundup for up to 2 years. The EU reaffirmed its approval for consuming GM maize designed for resistance to Roundup in 2019. This contradicted some studies into the short- and long-term toxicological effects of the same GMO or pesticide Roundup. Glyphosate is presently

authorized to be employed in the EU until 15 December 2022. The Glyphosate Assessment Group (AGG) has reviewed all the data supplied by those companies that seek renewed authorization. Consultations on the report will be held by the EFSA and the European Chemicals Agency (ECHA). The public will be able to participate in these discussions, which commenced in the first week of September 2021. Glyphosate's classification will be assessed by the Committee for Risk Assessment (CRA) of the ECHA according to the Classification, Labeling, and Packaging (CLP) Regulation. The EFSA will complete its review and publish its findings after the ECHA has approved its decision, probably late in 2022. The European Commission will determine whether or not to extend glyphosate depending on this risk assessment [86]. In short, the assessment method of GMOs is not standardized, and evaluations require a case-by-case approach. For GM food, the common technique has been to make a comparison to conventional counterparts. As a wider variety of plant organs can be used for animal consumption than for human consumption, and as storage conditions for GM forage products can be less strictly controlled and regulated than for GM food, a more thorough and careful assessment might be required for GM feed [8].

4. The Application of GMOs to Agriculture and Food Production

Following the development of biotechnological tools such as CRISPR-Cas, many research works aim to adapt them to potential industrial applications. Given the growing demand for food resources, agriculture is showing much interest in applying these technologies. The genetic modification of plants can be carried out by two mechanisms (Figure 5): adding genes to provide them with new traits or silencing particular genes by blocking the expression of undesirable features [15]. Since 1996, GM crops have been increasingly grown, with 190 million hectares worldwide in 2016 [14]. Agronomic traits, such as pesticide and virus resistance, herbicide and disease tolerance, and delayed ripening, were the first focus of GE in plants [87]. Most GM crops provide protection against insect herbivory and tolerance to herbicides such as glyphosate [88]. These two individual and combined traits represent >99% of land used to grow GM crops globally [89]. Nevertheless, scientists are interested in employing GE to create and produce plants with desirable characteristics such as superior quality or high nutritional content. For example, this includes crops with an enhanced fatty acid profile and biofortified food, such as Golden Rice. GM can also be useful for producing crops with commercial applications to promote human health, such as edible vaccines or pharmaceutical plants [87]. A review of some of the most relevant developed GM crops can be found below.

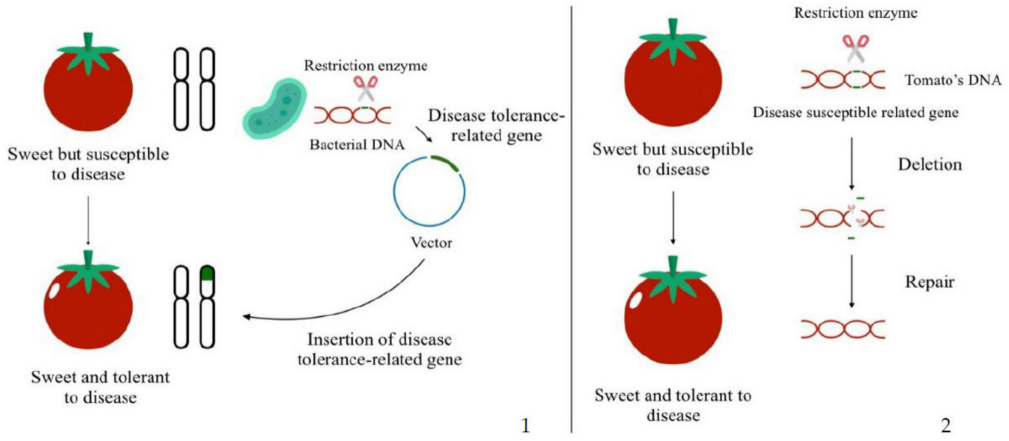

Figure 5. An illustration of the two main genetic modification methods: (1) gene addition and (2) gene silencing. Icons made by Freepik and Smashicons from www.flaticon.com (accessed on 1 December 2021). Adapted from [37].

4.1. Delayed Ripening

The first genetically engineered crop product to be commercialized was the Flavr SavrTM tomato [22]. Tomatoes only remain solid and ripe for a limited time period. The tomato lifetime can even be shorter than the time it takes to reach the market because softening can harm fruit while it is transported, hence the interest shown in delaying the softening. Until then, green fruit are picked and ripened artificially by ethylene treatment, which confers tomato their ripe color but not the full array of flavors. In the 1980s, some research studies revealed that enzyme polygalacturonase (PG) might be related to tomato softening because it degrades cell-wall pectin. The Californian company Calgene proposed developing a more resistant tomato to rotting by adding an antisense gene that inhibits PG accumulation in ripening tomatoes. In 1987, Calgene researchers identified and cloned a tomato PG gene and produced a GM tomato by inserting PG antisense DNA constructions. They expected to produce fruit that remained firm for long time periods by permitting it to be transported to markets, even after ripening. Some generated tomato lines exhibit only 1% PG compared to conventional ones. Based on the results obtained with field trials, in May 1994, the US Food and Drug Administration (FDA) approved Flavr SavrTM tomato commercialization [90]. The only two differences observed between Flavr SavrTM tomatoes and conventional ones were that fruit cell-wall pectin degraded more slowly and that tomato paste viscosity was greater [90,91]. Although demand was not low, its production ceased in 1997 due to high production and distribution costs [22].

Given the essential role that ethylene plays in ripening climacteric fruit, many researchers have paid attention to the genetic manipulation of those genes encoding the enzymes involved in ethylene biosynthesis. For instance, melons have short shelf lives because fruit ripening is caused by ethylene production. By inserting an antisense gene that inhibits the expression of ACC-oxidase (an enzyme involved in ethylene biosynthesis), a GM melon has been developed with flesh firmness enhancement and has an extended 30-day shelf life compared to the less than 12 days of conventional fruit [92]. Another example of GM crops for delayed ripening is banana. In developing countries, bananas are a staple food for millions of people, mainly because they are an important source of carbohydrates and nutrients. Delayed fruit ripening may be accomplished by reducing ethylene synthesis. Two genes, MaMADS1 and MaMADS2, have been functionally related to banana ripening. When repressing either gene (via antisense or RNA interference (RNAi)), a transgenic banana plant is created. It exhibits specific ripening delay and extended shelf-life phenotypes, including delayed color development and softening [93]. Delayed ripening allows the fruit to be picked from plants later, and this more natural ripening, which enhances fruit organoleptic properties and nutritional values.

4.2. Protection against Insects and Tolerance to Herbicides

In the 1970s, when it became evident that overusing chemical pesticides could pose serious negative consequences for human health and the environment, the FAO defined the Integrated Pest Management (IPM) concept. IPM is internationally recognized as a desirable plant protection standard that takes into account all the available pest control techniques and maintains pesticides and other interventions at levels that reduce or minimize risks for human health and the environment [88,94]. The plants that have been genetically modified to resist pests are a cornerstone of IPM and can be used in conjunction with other pest management techniques. As previously stated, most GE crops provide tolerance to herbicides (e.g., glyphosate, 2–4 D, or glufosinate-ammonium), protection against lepidopteran and/or coleopteran pests, or a combination of both traits [80]. Some advantages of adopting GM crops for insect management are generally acknowledged, such as the potential to minimize pesticide use or high pest specificity [88,95].

Halfway through the 1990s, the introduction of GM crops led to substantial pest control system modifications [96]. For a long time, *Bacillus thuringiensis*, a Gram-positive bacterium that produces endogenous crystals upon sporulation, has been employed as a biological pesticide. The proteins contained in these crystals are poisonous for some insect larvae,

mostly dipteran and lepidopteran species. Under the alkaline conditions of the insect midgut, the crystals break down and release proteins, which are proteolytically digested by proteases into less hazardous fragments (Figure 6). In 1985, the Belgian company Plant Genetic Systems was the first to develop GM plants with a tolerance to insects by inserting the crystal protein gene (bt2). This company created engineered tobacco plants that defend themselves from sensitive lepidopteran insects to the *B. thuringiensis* toxin [97,98]. This is how Bt-transgenic crops have been developed and cultivated since 1996 [96]. GM maize was one of the first transgenic crops to be commercialized. Resistant maize variants to glyphosate herbicides were produced by Monsanto, as well as Bt maize, a GM known to express one Bt toxin or more. Today, several crops show both glyphosate resistance, such as GM soybean, canola, cotton, sugar beet, and alfalfa, and insect resistance, which is conferred primarily by *B. thuringiensis* toxins and is found primarily in cotton, soybean, and maize. Furthermore, eggplant (*Solanum melongena* L.) is one of the most widely produced and consumed vegetables in Asia for its low cost, and Bt-transgenic eggplant crops have been grown in Bangladesh since 2014 [88].

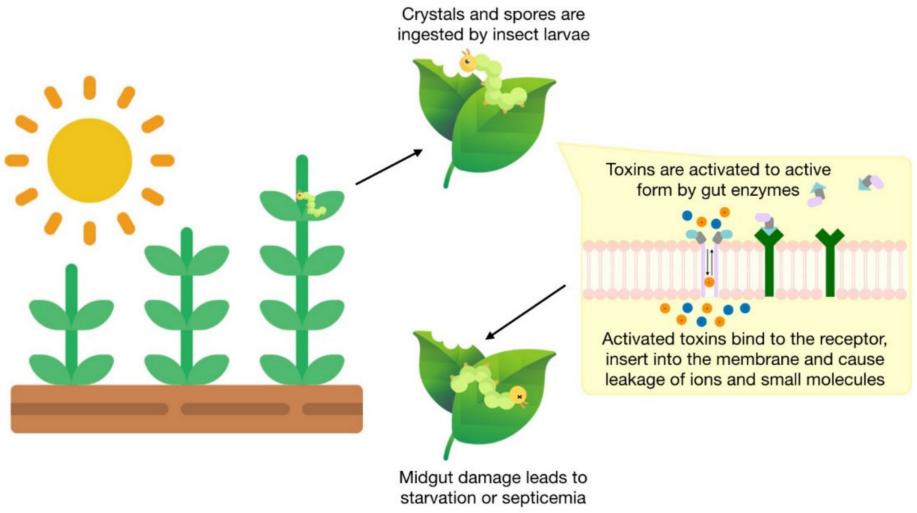

Figure 6. Mechanism of action of *Bacillus thuringiensis* toxin. Icons made by Freepik and Smashicons from www.flaticon.com (accessed on 1 December 2021). Adapted from [99].

Nowadays, farmers and consumers demand more guaranteed food safety. The main purpose of an IPM strategy is to support the sustainable production of high-quality crops while reducing environmental impacts attributable to pests. Although GM crops may seem a potential short-term solution to control pests, a long-term vision is necessary because, by means of herbicide and Bt tolerance traits, weeds and insects will inevitably display resistance with time. For this reason, one of the IPM plan objectives is to limit dependence on a single technology. The application of an IPM strategy offers fairly clear benefits, including reduced risks to human health and the environment, fewer applications of chemical pesticides, and more durable pest management in crop production systems. GM crops are a powerful tool in these sustainable and eco-rational IPM strategies. However, it is important to collect all the information and experiences acquired with GM crops to understand the limitations of technology to enhance the durability and versatility of IPM plans for future crops [88,96].

4.3. Virus-Resistant Plants

Viral infections are one of the most frequent reasons for smaller yields and substantial economic agriculture losses [100]. As viral infections in crops bring about 10–15% losses in worldwide yields, employing GE to create resistant plants to viral infections may be a solution to overcome this issue [15]. For example, viruses from the *Geminiviridae* family infect a wide range of plants worldwide, which include bean, maize, tomato, cotton,

pepper, and potato, among others. These viruses bring about considerable agricultural damage, which results in lower yields. Mosaic, leaf curling, mottle, vein yellowing, leaf yellowing, crumpling, and rugosity are just some of the signs of the diseases that geminiviruses cause [101]. As climate change globally affects insect vector distribution, with high levels of recombinations, rearrangements, and mutations of viral genomes, both the prevalence and severity of geminivirus-related diseases have significantly increased in the past 20 years [101–104]. These viruses will pose a significant threat to agriculture worldwide. The use of GE tools has emerged as an efficient possibility to achieve resistance against geminiviruses [15]. For instance, recent studies have shown the efficacy of the CRISPR-Cas system in developing resistant *Nicotiana benthamiana* [105]. Such findings indicate that this approach can be followed to create increasingly resistant plants to viral infections with time [15,101]. These methods are being extensively investigated to develop resistance to wide-ranging plant viruses. One example of such is GE tools, which have been employed with cucumbers to enhance resistance to two potyviruses and to three other viruses that cause severe cucumber damage. The *Potyvirus* genus accounts for a high percentage of vegetable viruses and is responsible for decreasing the marketability of many crops. The CRISPR-Cas system can limit pathogenicity and improve its tolerance against potyviruses, while no significant differences have been observed in dry weight, flowering, and growth between transgenic and wild-type plants, although the durability of this resistance should be further tested [15,106].

4.4. Physico-Chemical Crop Resistance

A number of plants depend on geographical locations and very specific climates to grow, which limits not only the crop viability of some regions but also more output. GE might be a way to help crops adapt to different growing circumstances [15]. For example, maize is grown mostly by applying dry farming practices, even though it does not well manage drought [107]. Recent research has shown that genome editing at a negative regulator of ethylene response, the ARGOS8 locus, generates drought-tolerant crops [108]. After being bruised or sliced, most crops' physical properties are lost. The expression of a particular polyphenol oxidase (PPO) gene causes *Agaricus bisporus*, commonly known as white button mushrooms, to turn brown. Recently, a group from Pennsylvania State University developed a deletion in the family of genes encoding PPO and created non-browning mushrooms [109].

4.5. Nutritional Improvement

Apart from the aforementioned improvements, GE technologies have been applied to increase plant nutritional value. The importance of nutrition and food in human health has drawn plenty of attention in recent years [15]. Enhancing crops' nutrient contents instead of adding nutrients to food during their processing is known as biofortification. Recent studies have shown the value of biofortification with conventional breeding as a successful nutrition and public health intervention in developing countries in SE Asia, sub-Saharan Africa, and Latin America. GM foods that provide nutritional benefits are extremely promising for fighting malnutrition (Table 3) [110]. For instance, retinol or vitamin A is a fat-soluble micronutrient contained mainly in eggs, liver, and butter. Green and yellow vegetables also produce vitamin A precursors, such as b-carotene and other carotenoids. As too much retinol can cause toxic excess in vitamin A, vegetable carotenoids have the advantage over retinol from animal sources because carotenoids can be converted into retinol depending on metabolic requirements. Vitamin A deficiency (VAD) may cause several diseases such as night-blindness, xerophthalmia, bone growth deficiencies, or keratomalacia or may weaken the immune system and can lead to serious problems, depending on the patient's age. Children are the most vulnerable population group, with a death rate of up to 50%. According to the WHO, VAD is a global public health concern, especially for children, and it affects 140–250 million preschool children in over 118 countries [87]. Rice is the major staple food for hundreds of millions of people worldwide. The edible part of rice grains

contains starch granules and protein bodies but lacks several essential nutrients, such as carotenoids, that maintain health. This makes VAD related to rice-based diets a serious public health problem in at least 26 countries, including areas in Asia, sub-Saharan Africa, and Latin America [111]. In 1984, the Golden Rice concept was first suggested, which is an engineered rice in which the endosperm would be rendered yellow through b-carotene accumulation (pro-vitamin A) [89]. The first Golden Rice was engineered by inserting the PSY gene from *Narcissus pseudonarcissus* and the bacterial phytoene desaturase (CrtI) gene from *Erwinia uredovora*, which can catalyze phytoene to retinol precursors. However, according to both the FAO and WHO, the carotenoid content of Golden Rice did not meet the minimum nutritional requirements, not even if consumed as staple food. Nevertheless, the biotechnology company Syngenta developed Golden Rice2 in 2005 by choosing the maize PSY gene instead of the previously used PSY genes. This new crop increased carotenoid content by up to 23-fold compared to the original Golden Rice and came close to a realistic level to palliate children's VAD [87,112]. Because of its high carotenoid content, Golden Rice could act as a possible VAD treatment and could favorably influence human health. As such, its adaptation to local cultivation is relevant and is under study [87].

Table 3. Biofortification of GM crops.

GM Crop	Substances Involved	Effect	Molecular Target
Golden Rice2	B-carotene	Anti-VAD	PSY [87,112]
Tomato	Lycopene Flavonoids Carotenoids	Antioxidant Anticancer	DET1 [87,113]
Indigo Rose Tomato	Anthocyanins	Protection against biotic and abiotic stressors	-SIAN2/SIMYB75 -SIANT1 -SIAN2-like/Aft [114]

Another example of GM crops in which nutritional value is improved could be by altering the fatty acid profile. The health benefits associated with a diet containing omega-3 long-chain polyunsaturated fatty acids are a well-known fact of life. It is scientifically proven that they reduce the risk of cardiovascular disease, act as positive anti-inflammatory lipid mediators, and play roles in brain and retinal functions. Currently, these fatty acids are obtained mainly from oceans via the wild capture of marine fish and shellfish [115]. In the late 1990s, interest began to be shown in engineering plants to accumulate omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs). These omega-3 LC-PUFAs include eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), which are absent in higher plants. The biosynthesis of EPA and DHA involves many enzymes that are not expressed in higher plants. Some decades ago, the scientific community did not know the molecular identity of these biosynthetic activities, but the discovery of desaturases and elongases required synthesizing EPA and DHA to make the expression of these omega-3 LC-PUFAs in plants possible. In more recent years, studies have shown that canola can be an alternative to fish consumption [89].

Apart from producing biofortified crops to combat malnutrition, biotechnology enables the cultivation of healthier foods for the general public (Table 4). Recently, there has been growing concern about the production of acrylamide while frying. A Maillard reaction occurs between certain amino acids, including free asparagine, and reduces sugars when certain starchy foods with low humidity are at temperatures over 120 °C. The product of this reaction is an organic low-molecular-weight compound that is highly soluble in water. It browns food, affects its taste, and has been recently classified by the International Agency for Research on Cancer (IARC) as a probable human carcinogen (Group 2A). This compound is known as acrylamide, and, to date, the results from studies with humans have been inconclusive about its toxicity [116]. Potatoes are the fourth largest staple crop in the world after maize, wheat, and rice. Potatoes are carbohydrate-rich food, of which 60–80% of

dry matter is starch, and have been considered an unhealthy food source for their relatively high glycemic index. Recently, the impact of potato GM on acrylamide formation has been studied. A research team developed a transgenic potato variety, known as Snowden, which overexpresses pyruvate decarboxylase from Arabidopsis. This transgenic potato appeared to increase the resistant starch and phosphorus contents of potato dry matter. When stored at 5 °C, a 69% reduction in acrylamide production was observed in potato chips [117]. The J.R. Simplot Company developed the genetically modified Innate potato, which was approved by the US Department of Agriculture in 2014 and by the US FDA in 2015. Innate potato uses RNAi gene silencing technology to regulate the expression of the genes responsible for the enzymatic darkening process, which makes them less susceptible to darkening and to the onset of black spot from bruising by knocks or pressure while stored. The latest studies also reveal that Innate potatoes contain 52–78% less acrylamide when fried or baked at high temperatures because they have lower levels of asparagine and reduced sugars. The FDA and USDA have extensively reviewed Innate potatoes and indicate that they are as safe as a conventional potato. For this reason, the FDA thinks that adopting these new potato varieties could serve as a method to help the general public to reduce its dietary acrylamide intake [118].

Table 4. Healthier crops obtained through GE.

GM Crop	Substance	Risk	Modification	Effect
Snowden Potato	Acrylamide	Carcinogen (Group 2A)	Pyruvate decarboxylase overexpression	69% reduction [109]
Innate Potato	Acrylamide	Carcinogen (Group 2A)	RNAi gene silencing technology	52–78% reduction [110]
Wheat	Gluten	Coeliac disease	Gliadin content reduction	97% reduction [111]

In addition, GM crops can be used as a solution to eliminating allergens in food. Coeliac disease (CD) is an immune disorder caused by a reaction to gluten, a group of various proteins found in wheat and other grains that primarily affect the small intestine and cause classic gastrointestinal problems, such as chronic diarrhea, abdominal distention, or malabsorption. In recent years, human pathologies associated with grain proteins have increased worldwide, and the only way to treat this pathology is by eating a lifelong gluten-free diet. Nevertheless, a gluten-free diet is quite complicated to follow because wheat is a staple food and gluten-free foods tend to be much more expensive. One research group has developed wheat bread that is potentially suitable for celiac patients and other gluten-intolerant individuals. This bread is made by wheat flour with a very low gliadin content and the main epitopes of wheat gluten that induce an immune response in celiacs. Reduced-gliadin breads show similar organoleptic and nutritional properties to those of normal flour but with up to 97% lower gliadin content. Hence, this product can be consumed by the general celiac population [119].

As described herein, significant progress has been made in recent years in using transgenic plants as platforms to create a range of health-beneficial compounds. Nonetheless, public acceptance of GM crops is one of the biggest obstacles to their commercial application.

4.6. Functional Food: Edible Vaccines

Humans have used plants as therapeutic products for thousands of years because they are a reservoir of valuable pharmacological compounds [87]. Plants have recently become an appealing platform for edible vaccine production. As conventional vaccine development is lengthy and costly, disease outbreaks might become extremely difficult to manage in

many situations. For example, in the first 6 months of the COVID-19 pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused more than 1 million deaths and wreaked havoc on both the global economy and social order. To prevent further morbidity and mortality, developing an effective vaccine and antiviral therapy against this virus is a pressing need [120]. Edible vaccines seem a superior alternative, especially in developing countries, as they need no pre-administration treatment or purification, are less costly to produce, are simpler to administer, pose no storage difficulties, and are bio-friendly [121]. The Spike (S) protein gene or a component of Spike, such as the S1 subunit, can be cloned into a plant expression vector. The generated transgenic plants may be eaten and readily and orally administered to immunize humans against the newly emerged virus [120].

Additionally, recent studies have shown that edible vaccines stimulate both systemic and mucosal responses, and the area required for oral vaccine production for all infants worldwide covers only 200 hectares [122]. Most studies have used cultivated potatoes, which appear to be an appropriate model for producing vaccines against tetanus, diphtheria, or hepatitis B [121]. However, potatoes might not be the best choice of edible vaccines because cooking can weaken most antigenic proteins [123]. Rice is another plant species used to develop edible vaccines. It might have a severe public health impact because rice is a staple food and shows a high antigen expression. Banana is also used frequently for producing edible vaccines because it does not need cooking. Tomatoes, maize, tobacco, bananas, carrots, and peanuts are plant species with a much brighter future as edible vaccines (Figure 7). Nevertheless, many plant species, such as lettuce, papaya, quinoa, and tobacco, are being studied to create edible vaccines. Of the main diseases for which food vaccines are developed, rabies (spinach), hepatitis B (potato and lettuce), cholera (rice), diarrheal diseases (potato and maize), and anthrax (tomato and spinach) are noteworthy. In 2005, the WHO held a meeting about the regulatory assessment of plant-based vaccines, which concluded and established that existing guidelines for the development, evaluation, and use of vaccines, following conventional methods, can be applied to produce edible vaccines. Although the discovery of edible vaccines is one of the main breakthroughs on the biotechnology branch, the main challenge is for the public to approve them. As their benefits are prominent enough to overcome their side effects, appropriate research is necessary to make the better control of infectious diseases possible [121].

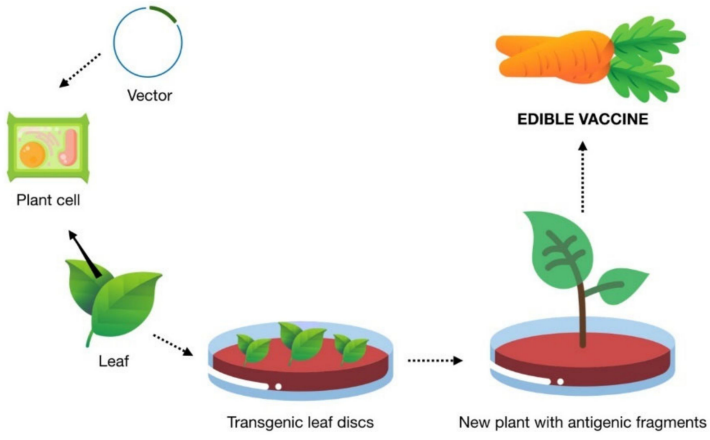

Figure 7. Development of edible vaccines. Icons made by Freepik and Smashicons from www.flaticon.com (accessed on 1 December 2021). Adapted from [124].

5. The Future of GM Products

Agriculture is a relevant sector for the world's economy, and it stretches far beyond food production. One of the most significant social, economic, and scientific challenges of the modern world is its consistently growing human population. It has been estimated that the global population will reach 9 billion people by 2050. As current food production levels will not suffice to meet food demands, achieving global food security poses a serious chal-

lenge. The easiest way to overcome this is to increase the acreage of farmable land, but the vast majority of arable agricultural land is unavailable because it is already used. Climate change is another limiting factor that reduces agricultural productivity with its extreme temperatures, high salinities, floods, and acid conditions. Throughout history, humans have made significant food production improvements. The introduction of chemical fertilizers, pesticides, and herbicides has boosted crop yields. In the 1940s, the "Green Revolution" brought about a further substantial increase in crop yields. Nowadays, agrobiotechnology has been proposed as a measure to supply the world's growing future population and to serve as a solution to the "not enough food" problem. GE and creating GM crops are promising tools for agriculture as they can help to address some of the challenges that lie ahead. There are further benefits from GM crops, such as bigger crop yields without having to extend cultivated areas and reduced fertilizer use and greenhouse gas emissions. Eliminating GM crops from cultivation would sharply increase the global cultivation area at the expense of rainforests, which would intensify greenhouse gas emissions that would, in turn, aggravate climate change [125]. Apart from all these advantages, certain economic benefits are implied. Higher yields, improved productivity, and cost reductions from GM crops have resulted in global economic advantages of USD 15.4 billion in 2015 and USD 167.8 billion from 1996 to 2015 [126].

The public accepting GM crops is one of the main obstacles to commercial application. The development of metabolomics to provide a comprehensive qualitative and quantitative overview of the metabolites present in food could slowly gain public favor [87]. However, consumers may still be skeptical about GM food despite accumulating scientific data. Studies have attempted to analyze changes in attitudes toward GM food by focusing on providing more information about GE and its risks and benefits. After acquiring information on the risks and benefits of GM products, recent public surveys appear to show more acceptance. In most cases, the rejection is based on moral intuitions and scientific arguments suggesting transgenic foods are often not effective. As this strategy proved ineffective, an entirely different one was attempted. Recent studies have worked on addressing the moral GE problem by means of another emotional concern. Respondents were informed about serious global problems using the example of diets lacking vitamin A and how Golden Rice could prevent child deaths and blindness. As the respondents faced these two moral problems, their acceptance of GE grew. Therefore, perhaps the interventions made with the population have not been strong enough to counteract their strongly moralized attitudes toward GMOs [34].

Nowadays, a wide range of GM vegetables is available on the market, mostly soybean, maize, cotton, and canola, as well as other GM species such as rice, squash, papaya, sugar beet, potato, and tomato. However, the creation of new transgenic crops is being investigated, such as apple, mango, pineapple, banana, sweet potato, barley, coconut, and lettuce. As most marketed GM crops now offer tolerance to herbicides or protect from plagues, many benefits are being studied. It is important to note that GM crops are one of the avenues to help to overcome the world's food crisis and its environmental problems. Healthcare issues are also a crucial matter, mainly for people in underdeveloped areas. For example, Golden Rice can provide tangible benefits to meet socio-economic needs by alleviating the human costs associated with blindness and other vitamin A-related disabilities. GM crops can also serve as nutraceuticals and edible vaccines without requiring broad-scale industrial facilities [79]. For this reason, priority should be given to food safety and not to the methods by which new traits and properties are incorporated. In the near future, scientific progress will lead to GM plants with new traits, and the development of metabolomics will allow better risk assessments. As in any aspect of life, there is no zero risk in food, so it should not be generalized that all transgenic foods are good or bad. GM food should be treated as traditional foods. Finally, the debate should move on to the scientific field rather than to an emotional one, and a risk–benefit analysis should be carried out prior to marketing a new product.

6. Conclusions

Today, only a few GM crops can be marketed as food. However, the application of GE techniques to develop GM crops could be used to address the new challenges of climate change, sustainability, and global food safety. Although more and more GM crops are being launched on the market, some consumers and the scientific community still reject them. Given the difficulty of assessing the long-term risk of consuming GM crops, one of the main problems is the likelihood of them actually posing a potential risk to human, animal, or environmental health. Classically, GMOs have been associated with different risks, including toxicity problems, development of allergies, tumor development, infertility, and the possibility of horizontal transfer of transgene(s) to the environment or to other species. However, there is insufficient scientific evidence to state that they actually harm health. The OECD has defined the Substantial Equivalence principle, according to which GMOs should be considered safe as conventional foods. Although the probability of horizontal gene transfer is quite low, the use of genes that confer antibiotic resistance as selectable markers has been banned. Many products on the market, such as processed meats or alcohol, are included on the WHO list of carcinogenic foods, but there are still fears of transgenics. Population surveys still show a negative attitude toward GMOs due to moral aspects.

Most GM varieties on the market today are herbicide- and pest-resistant, and the majority serve as food for animals. However, a wide variety of crops is being studied to create plants with desirable traits, such as delayed maturation, biofortified vegetables, healthier plants, and edible vaccines. All these crops would offer marked economic, environmental and food security, and human health benefits. In the last few years, significant progress has been made that not only demonstrates the feasibility of using transgenic plants as platforms to make a range of health-beneficial compounds but also moves further along the translation pipeline, ultimately toward regulatory approval, commercialization, and consumer intake. It is thought that developing metabolomics will help to improve the safety assessment of transgenic foods, which will gradually lead to more consumer acceptance due to the forthcoming borderline situations owing to climate change and high food demands.

As described throughout, GM foods are not only useful to cover future generations' nutritional deficiencies but can also better respect climate change and offer a benefit that goes beyond such general aspects, which the general public mainly ignores. Hence, this reported consumer health benefit should be made known to the general public to reverse its current rejection and to dispel phobias related to GMOs.

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