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DYNAMICS OF GENOME EDITED PRODUCTS IN THE WORLD MARKET FOR FUTURE FOOD SECURITY : A REVIEW

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ABSTRACT

Genome edited products have the capacity to tackle a wide array of significant issues, including food security, nutrition, health, diversified agriculture, climate change, and environmental sustainability. Through the utilization of genome editing techniques, we have the ability to enhance the food and nutritional security of our expanding population while simultaneously promoting environmental sustainability. There has been a substantial global development of market-oriented genome edited products in agricultural crops, animals, and human health. These products are renowned for their precision, effectiveness, and targeted approach. Among the various genome editing techniques, CRISPR/Cas9 technology has particularly gained prominence in the agriculture sector, leading to the creation of diverse market-oriented agri-food products. Its affordability has also made it accessible to developing countries, thereby increasing its market share compared to other techniques on a global scale. However, the economic impact of genome editing products will ultimately depend on their availability, especially in low- and middle-income countries. It is crucial to ensure that these products are accessible to all individuals in order to maximize their potential benefits. This article provides an overview of the current and potential use of genome editing technologies in the development of market-oriented edited products.

Key words : Genome editing, Agri-food, Market-oriented products and World market.

Introduction

It is estimated that the global population will increase by 25% and exceed 10 billion in the next three decades (Hickey *et al*., 2019). As a result, there is a growing necessity to enhance food production by up to 53% (FAO, 2018; 2022). To tackle this challenge, it is crucial to develop novel crop varieties that can withstand both biotic and abiotic stresses, utilizing innovative methods (Abdul Fiyaz *et al*., 2020). While the Green Revolution has significantly boosted food grain production and alleviated global hunger and poverty, it has also introduced new obstacles such as the excessive use of agrochemicals and monocropping (World Resources Institute, 2019; FAO, 2022). In order to meet the rising demand for food in a sustainable manner, it is necessary to enhance current productivity and quality (Ray *et al*., 2012; Hickey *et al*., 2019). Plant breeders are diligently working towards improving crop productivity and developing new varieties that yield higher quantities, possess greater nutritional value and exhibit tolerance to both biotic and abiotic stresses, as well as resilience to climate change (Hickey *et al*., 2019). Despite the development of transgenics in various crops, their full potential remains untapped due to strict regulations. To achieve genetic improvement and create new crop varieties, it is imperative to utilize innovative biotechnological tools (Salgotra *et al*., 2015). Modern plant breeding and biotechnological techniques, such as genome editing and genetic transformation, play a crucial role in the development of new crop varieties with enhanced traits. However, conventional breeding

methods have shown limited success in improving crop varieties controlled by complex traits. Therefore, advanced biotechnological techniques, including gene editing tools, can be employed for the genetic improvement of complex traits (Mushtaq *et al*., 2018).

Advancements in biotechnology, such as high-throughput whole-genome DNA sequencing, pangenomes and genome editing, have significantly improved the genetic transformation of elite crop varieties, resulting in enhanced quality traits (Richardson *et al*., 2014; Lowe *et al*., 2016). Genome editing techniques enable targeted and precise modifications in crop genomes, leading to the enhancement of desirable traits, including those crucial for food security (Gaj *et al*., 2016; Wang *et al*., 2016). These gene editing methods have gained widespread acceptance due to their similarity to products/varieties developed through conventional breeding programs (Sikora *et al*., 2011; Grohmann *et al*., 2019; Mushtaq *et al*., 2019). Crop varieties developed through gene editing techniques are considered equivalent to those developed using traditional methods, while also requiring less time and fewer biosafety regulations (Fig. 1). These editing techniques offer a high level of precision and predictability in modifying crop genomes to achieve desired traits (Bayer *et al*., 2020; Kevin *et al*., 2022). Moreover, the adoption of these new technologies depends on their reproducibility and the significant impact of their results. Genome editing techniques have proven to be highly effective in plant research, facilitating the modification and introduction of novel genes into various crop species (Mushtaq *et al*., 2018). However, the efficacy of genome editing technologies in targeting specific traits of plant genomes relies on distinct protein-DNA interactions. Specifically, CRISPR-Cas, a genome editing technique, has simplified the process of efficiently targeting protein domains in areas of interest within a genome, revolutionizing the field of biotechnology for sequence modification (Doudna and Sternberg, 2017). Generally, the genome editing process involves two components: targeting a DNA site of interest within the nucleus of a living cell and editing it. However, the endogenous cellular DNA replication and repair precisely secures the editing product.

Genome editing, particularly the CRISPR-Cas system, has emerged as an exceptionally effective technique for altering the genetic composition of various crop species (Upadhyay, 2021). Over the last decade, genome editing methods have been utilized to enhance different characteristics in a wide array of crops. Recent advancements in genome editing technologies have led to a flourishing market, with a total value of USD 5.1 billion in 2021 and it is projected to reach USD 11.7 billion by 2026 (FAO, 2022). In comparison to genetically modified crops (GMOs), gene editing techniques offer certain advantages due to less stringent regulations and societal concerns (He and Krainer, 2021). GMOs involve

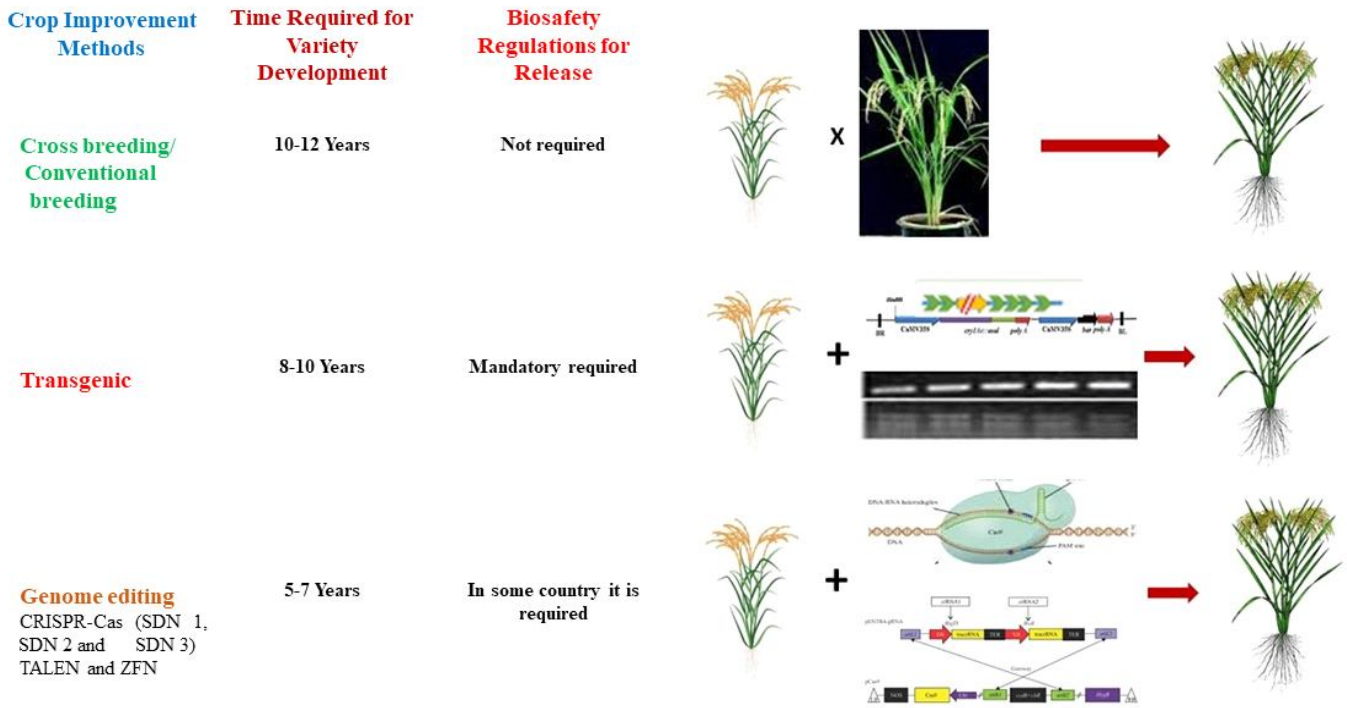

Fig. 1 : Advantages of genome editing technique CRISPR-Cas (SDN 1, SDN 2 and SDN 3) over transgenic and conventional breeding method.

the introduction of foreign genetic material into the host organism, whereas genome editing does not. However, both approaches aim to generate crop variants with improved yield, enhanced quality and increased resistance to biotic and abiotic stresses. It is crucial to acknowledge that GMOs have been linked to the emergence of pesticide and herbicide-resistant pests and weeds, as a consequence of selective pressure (Bawa and Anilakumar, 2013). If these genetically modified cultivars are extensively cultivated, there is a high probability of strong selective pressure in the environment, leading to the evolution of resistant insects within a few years and potentially undermining the intended benefits of transgenic crops. Concerns have been raised regarding genetically modified (GM) foods due to the potential risks associated with toxins, allergens, and genetic hazards. Furthermore, there is uncertainty surrounding the possibility of pest-resistant traits in GM crops transferring to their weedy relatives, resulting in the emergence of resistant and increased weeds (Bawa and Anilakumar, 2013). However, the primary environmental concerns associated with GM foods include: i) the risk of outcrossing, where genes from genetically modified organisms (GMOs) can transfer to wild plants and other crops; ii) the adverse impact on insects and other species; and iii) the reduction in other plant types, resulting in a loss of biodiversity.

CRISPR/Cas9, ZFN and TALEN are among the gene editing techniques available. However, CRISPR/Cas9 has emerged as a powerful and precise tool for creating natural and spontaneous mutations or genetic variations. Its ability to achieve precise, cost-effective, and heritable desired mutations has made it a promising technique in genome editing systems. Additionally, CRISPR/Cas9 offers advantages such as multiplexing, prime editing, and base editing. Recent advancements in the specificity, efficiency, precision, and delivery of DNA and RNA base editors have further enhanced the potential of these technologies in crop improvement (Porto *et al*., 2020). As a result of progress in genome editing tools, gene sequences have been altered across various organisms, including important agricultural plants, leading to the development of diverse products. Initially, genome editing was primarily utilized in government research and academic institutions. However, this technology is now being commercialized for the production of potentially transformative diagnostic tools (Prasanta *et al*., 2023).

Various stakeholders, including consumers, researchers, developers and governments, play pivotal roles in the worldwide marketing of gene editing. Their contributions have a significant impact on the economy across diverse sectors. While public sector research programs primarily concentrate on academia, private sector initiatives are directly influenced by market demands and profit-oriented objectives (FAO, 2022). The advancements in genome editing research and its implications have fostered collaborations between academic institutions and industry players for research and development endeavours. Notably, numerous private companies, such as Editas Medicine Inc., Precision Bio Sciences Inc., New England Biolabs Inc., Sangamo Therapeutics Inc., CRISPR Therapeutics AG, Agilent Technologies Inc., Integrated DNA Technologies Inc., Gen Script Biotech Corporation, Merck KGaA and Thermo Fisher Scientific Inc., are driving the expansion of the gene editing product market. These companies actively engage in the development of genome-edited products for plants, animals and innovative human medicines. This article aims to provide an overview of the current trends in genome editing products within the global market. The review article explores various gene editing techniques, with a specific emphasis on CRISPR/Cas, their application in product development and their potential in the global market.

Genome Editing Technologies

Genome editing techniques have revolutionized the ability to manipulate specific locations within the genetic makeup of crop plants, resulting in a wide range of modifications such as deletion, site-directed insertion, substitution, or targeted mutagenesis (Kim *et al*., 2017). One of the primary methods employed in gene editing involves the creation of site-specific double-strand DNA breaks (DSBs), which are subsequently repaired through either error-prone non-homologous end-joining (NHEJ) or error-free homology-directed repair (HDR) pathways. Currently, there are three main genome editing techniques utilized to generate site-specific DSBs, namely CRISPR/Cas9, ZFN, and TALEN, each possessing their own distinct characteristics and challenges (Kim *et al*., 2017).

CRISPR/Cas9 employs three types of nucleases, known as site-directed nuclease type 1 (SDN1), site-directed nuclease type 2 (SDN2) and site-directed nuclease type 3 (SDN3), for the purpose of editing crop plants. In SDN1, a frameshift mutation occurs, resulting in a double-stranded DNA break. This technique involves the random addition or deletion of nucleotides, followed by repair through NHEJ. The SDN1 mutation is also referred to as a point mutation within the organism's genome. On the other hand, SDN2 involves the replacement, addition, or deletion of specific nucleotides using a synthetic DNA template within the double-stranded sequences. The resulting break is repaired

through NHEJ (Li and Xia, 2020). Loss of function in the edited gene sequence can occur due to frameshift mutations and the error-prone nature of NHEJ repair at specific genomic regions (Van Vu *et al*., 2020). In SDN3, the entire gene sequence or a segment of the gene is modified at a specific site within the genome, followed by repair through the NHEJ system, ultimately leading to the development of a transgenic product.

The Consultative Group on International Agricultural Research (CGIAR) and developing nations, such as India, are currently focusing on utilizing SDN1 and SDN2-based edits to enhance economically significant traits in various crop varieties, including rice, banana, maize, potato, wheat, yam and cassava. A recent advancement in gene editing within the SDN1 system involves the fusion of a nucleotide deaminase with a non-functional Cas9, resulting in the conversion of a GC base pair to an AT base pair and vice versa, without causing any damage to the genome (Shimatani *et al*., 2017; Li *et al*., 2018; Molla and Yang, 2019; Zhang *et al*., 2019). Base editing, on the other hand, involves the utilization of components from CRISPR systems and other enzymes to directly introduce point mutations into cellular DNA or RNA, without creating double-stranded DNA breaks (DSBs). Cytosine base editors (CBEs) are capable of converting a C › G base pair into a T › A base pair, while adenine base editors (ABEs) can convert an A › T base pair to a G › C base pair (Rees and Liu, 2018). This technique of introducing single-nucleotide variants (SNVs) into DNA or RNA within living cells represents a recent breakthrough in genome editing. Given that approximately half of known pathogenic genetic variants are attributed to SNVs, base editing holds immense potential for the treatment of numerous genetic diseases, either through temporary RNA alterations or permanent DNA modifications. Furthermore, an improvement to the CRISPR-Cas9 tool is the introduction of prime editing, which is a precise genome-editing technology that enables all possible base-to-base conversions, as well as small insertions and deletions, without the requirement of DSBs or donor DNA templates (Anzalone *et al*., 2019). Prime editing is the first of its kind and utilizes a modified Cas9 enzyme coupled with an engineered reverse transcriptase, along with a prime-editing guide RNA (pegRNA) that specifies the target site and encodes the desired edit (Anzalone *et al*., 2019). This advancement in gene editing technology opens up new possibilities for precise and efficient genome modifications. The gene editing technologies are very diverse, which are applicable in different fields such as, crop improvement, animal and human health, etc. that are being commercialized at large scale (Sauer *et al*., 2016).

The CRISPR/Cas9 tool is a widely used genome editing technique that has revolutionized site-specific gene manipulation in genomes, leading to the development of precision breeding. This innovative technology has enabled the efficient editing of crop genomes, saving time and resources. However, despite its potential, genome-edited crops are still primarily in the experimental stage. To fully harness the benefits of genome editing in agriculture, it is crucial to establish rational regulations and raise public awareness to gain acceptance for these crops in the market (Scheben and Edwards, 2018). Precision crop improvement programs have been initiated through the selection of agriculturally important traits and their genetic enhancement using gene editing technology. Although a few crops have been successfully genome edited, the availability of low-cost high-throughput sequencing technology has allowed for the sequencing of numerous crops (Scheben and Edwards, 2018). However, a major challenge lies in identifying the close association between genetic markers and specific agronomic traits from the vast amount of sequence data. The integration of large-scale data is essential to link genotypes with specific traits and identify candidate genes for the development of genome-edited crops. The widespread adoption of genome editing technology is hindered by the limited efficiency of delivery systems. Currently, these systems are inefficient and restricted to only a few crop species, posing significant challenges to the technology's application. To overcome these limitations, the development of efficient delivery systems, such as tissue culture-free methods, and genotype-independent systems is necessary to enhance the adoptability of genome editing technology (Chen and Gao, 2020).

One of the challenges faced in genome editing technologies is the limited number of specialized laboratories engaged in crop precision breeding programs. Some of these laboratories employ CRISPR/Cas9 techniques, utilizing single guide RNA (sgRNA) sequences and the Cas9 gene (Doudna and Charpentier, 2014). However, gene editing techniques still rely on time-consuming plant tissue culture and extensive analysis of sequencing data to identify desired agronomic traits (Hickey *et al*., 2019). The development of new crop varieties necessitates multiple generations of populations, which is a time-intensive process. To address this, Hickey *et al*. (2019) introduced speed breeding at Queensland University in Australia, enabling plant breeders to cultivate crop varieties under controlled conditions. This technique involves raising genotypes in controlled environments and accelerating physiological processes such as flowering

Table 1 : Comparison of the clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9), transcription activator-like effector nuclease (TALEN) and zinc finger nuclease (ZFN) techniques.

Particulars	Genome editing techniques		
	CRISPR/Cas9	TALEN	ZFN
Tools	CRISPR/Cas9 is an RNA based defence mechanism and composed of crRNA and trancRNA	TALEN is made from chimeric nucleases and composed of TAL DNA effector (TALE) cleavage domain	ZFN is made from zinc finger nucleases and composed of non specific DNA cleavage from FoKI restriction endonucleases
Basis	RNA based	Protein based	Protein based
Use for RNA editing	Yes	No	No
Origin	Derived from bacteria	Man made	Man made
Efficiency	Low	Moderate	Higher
Specificity	18-30nt	30-36nt	23nt
Multiplexing editing	Easy	Easy	Easy
Off-target efficiency	Low	Low	Higher
Cost	Low	High	Low
Application	Cell line editing, animal genome editing and plant genome editing	Cell line editing, animal genome editing and plant genome editing	Cell line editing, animal genome editing and plant genome editing
End user	Private companies, academics and government research institutes	Private companies, academics and government research institutes	Private companies, academics and government research institutes

and photosynthesis through optimization of day length, light intensity, and temperature. By employing this technique, researchers can achieve 4-6 generations in a year, as opposed to a single generation in normal field conditions or 2-3 generations in standard greenhouse conditions. Speed breeding has been successfully implemented in various crops, including wheat, canola, and barley (Abdul Fiyaz *et al*., 2020). However, a novel system called "Express Edit" has been implemented to expedite the varietal development program (Haroon *et al*., 2020). The "Express Edit" approach combines speed breeding with genetic engineering tools to reduce the generation time. In this system, specific components of the CRISPR system, such as sgRNA and Cas9, can be directly applied to the plants without the need for plant regeneration in laboratories. Consequently, "Express Edit" overcomes the obstacles associated with in vitro manipulation of plant materials. In the "Express Edit" approach, a solution containing the Cas9 gene and sgRNA sequences can be sprayed directly onto various plant parts, including leaves and flowers (Hickey *et al*., 2019). The resulting progeny with segregating traits can then be screened and plants that possess the new trait but lack the Cas9 gene can be identified. Alternatively, "CRISPR-ready" plants that still contain Cas9 can undergo additional rounds of editing by applying sgRNA for different gene targets (Hickey *et al*., 2019). In the CRISPR/Cas9 genome editing technique, the Cas9 enzyme is guided by the sgRNA to a specific DNA site, where it cleaves the DNA. During the segregating generation, genotypes that exhibit new traits but do not harbor the Cas9 gene are selected. The "CRISPR-ready" plants containing sgRNA can be further utilized for genome editing of other genes using speed marker-assisted backcrossing (Hickey *et al*., 2019; Haroon *et al*., 2020).

Advances in Development of Market Oriented Genome Edited Crops

Genome editing techniques offer a more precise means of modifying a plant's genome compared to other breeding methods. This advancement has the potential to significantly reduce the time required for breeding new crop varieties and also decrease the costs associated with research and development. The application of genome editing technology extends to a wide range of challenges, including the development of durable resistances to both biotic and abiotic stresses, as well as the enhancement of quality traits in various crops. In recent times, there has been a growing emphasis from researchers and policymakers on the need for increased investments and

advancements in the field of genome editing. Consequently, many countries regularly allocate funds to government and academic institutions to conduct in-depth research in this area. For instance, the United States government recently announced a financial support of USD 15 million to bolster genome editing projects in agriculture, health and the environment. Additionally, these genome editing programs receive further assistance from businesses, research partners, and local and provincial governments, amounting to more than USD 29.7 million (FAO, 2022). The systematic institutional and academic research in gene editing has resulted in the development of market-oriented products in various crops, ornamentals and human medicines. This trend is expected to significantly expand the market for genome-edited products and raw materials for future research purposes. Currently, market-oriented genome editing products are being developed worldwide to meet the demands of the global market (Modrzejewski *et al*., 2019). Through genome editing techniques, traits that are desirable for the market, such as herbicide resistance, biotic and abiotic stress tolerance, enhanced nutritional value, and aesthetic appeal, can be modified. Furthermore, genome editing techniques are versatile, cost-effective, and feasible for improving the quality of staple foods. This enables the enhancement of nutritional values in food crops, oilseeds, and floricultural crops without the introduction of any foreign genes. The utilization of genome-editing crop improvement programs has proven to be highly effective in various crops, including tomato, wheat, maize, rice, soybean, peanut, banana and more (Table 2). Currently, genome editing technologies, specifically CRISPR/Cas and its enhanced versions are successfully employed in enhancing orphan crops as well. The newly developed plant varieties based on CRISPR-Cas are virtually indistinguishable from those achieved through traditional breeding methods. This technique has facilitated the identification of novel alleles that exhibit improved phenotypes, which are highly favored by both plant scientists/breeders and consumers (Venezia and Krainer, 2021).

Malnutrition poses a significant challenge, especially in developing and underdeveloped nations, where over 340 million individuals suffer from one or more deficiencies in essential micronutrients (UNICEF, 2021; Kumar *et al*., 2022). The consequences of malnutrition have far-reaching effects on the long-term economic, developmental, health and social aspects of global communities. Additionally, consumers are increasingly concerned about the quality of crops due to their direct impact on human health through the delivery of vital nutrients such as proteins, fibers, vitamins, minerals and bioactive substances (Slavin and Lloyd, 2012). Biotechnological advancements have played a crucial role in improving the quality of various food crops to combat malnutrition (Kumar *et al*., 2022). While some countries have released genetically modified crops, particularly transgenic food crops, under strict biosafety regulations, many nations still prohibit the cultivation of GMO crops. However, genome-edited crops are being considered on par with conventionally bred varieties in most countries. Furthermore, compared to traditional breeding methods, genome editing techniques have demonstrated enhanced nutritional values in crops with significant efficiency and accuracy, without introducing foreign alleles (Ku and Ha, 2020). Among the various genome editing approaches, the CRISPR-Cas-based system has been extensively utilized to improve the quality traits of diverse crops. This system has been employed for enhancing the quality of rice, wheat, maize, barley, tomato, potato, rapeseed, fruits, and more (Table 3). Genome-edited techniques have successfully improved the shelf life, aroma, oleic acid content, anthocyanin levels, GABA content, and other desirable traits in various crops. These biofortified food products possess nutraceutical properties, which can be sold at higher prices in the market, ultimately enhancing their market value (Kumar *et al*., 2022).

Scope of Genome Editing in World Market

Genome editing technology has the potential to significantly contribute to the improvement of nutritional food security and environmental sustainability, as highlighted by Gordon *et al*. (2021) and Karembu (2021). This technology is known for its precise inheritance and its lack of harmful effects on human health. In fact, when compared to other techniques, gene editing approaches are comparable to conventional cross-breeding methods. Customers are particularly concerned about the enhanced safety and nutritional value of genome-edited crops, as well as the reduction of food waste. On the other hand, farmers prioritize the availability and affordability of seeds in the market, as well as the crops' enhanced resistance to biotic and abiotic stresses, as emphasized by Sedeek *et al*. (2019). The economic impact of genome editing on the market will largely depend on the accessibility of seeds, especially in developing and underdeveloped countries where this technology is not yet fully utilized. However, the adoption of genome editing technologies can potentially reduce the costs associated with farm management by requiring fewer inputs, thereby providing additional income to farming communities. Furthermore, these technologies are also contributing to the

Table 2 : Genome editing techniques used for development of genome-edited products resistance to different diseases.

Crop	Botanical name	Disease	Targeted gene	Gene function	Genome editing tool	Outcome	Reference
Rice	*Oryza sativa*	*Magnaporthe oryzae*	*OsERF922*	Encode ERF family transcription factor	CRISPR-Cas9	Edited lines showed considerably reduced blast lesions	Wang *et al.* (2016)
Rice	*Oryza sativa*	*Xanthomonas oryzae pv. oryzae*	*OsSWEET14*	Encode *SWEET* sugar transporter	TALEN	Enhanced resistance against Bacterial blight	Blanvillain-Baufumé *et al.* (2017)
Rice	*Oryza sativa*	*Rice tungro bacilliform virus (RTBV) and Rice tungro spherical virus (RTSV)*	*eIF4G*	Eukaryotic translation initiation factor 4G (*eIF4G*) is a protein involved in eukaryotic translation initiation	CRISPR-Cas9	Resistance against Rice Tungro disease	Macovei *et al.* (2018)
Rice	*Oryza sativa*	*Xanthomonas oryzae* pv. *oryzae*	*OsSWEET11, OsSWEET13, OsSWEET14*	Encode SWEET sugar transporter	CRISPR-Cas9	Broad spectrum resistance bacterial blight	Oliva *et al.* (2019), Xu *et al.* (2019)
Rice	*Oryza sativa*	*Xanthomonas oryzae* pv. *oryzae*	*OsSWEET14*	Encode *SWEET* sugar transporter	CRISPR-Cas9	Reduced lesion length	Zafar *et al.* (2020)
Cotton	*Gossypium hirsutum*	*Verticillium dahliae*	*Gh14-3-3d*	Negative regulators of BR signaling	CRISPR-Cas9	Enhanced resistance to disease	Zhang *et al.* (2018a)
Wheat	*Triticum aestivum*	*Blumeria graminis* f. sp	*TaMLO*	Susceptibility (S) gene involved in powdery mildew disease	CRISPR-Cas9 and TALEN	Enhanced tolerance to disease	Wang *et al.* (2014), Wang *et al.* (2018b)
Wheat	*Triticum aestivum*	*Blumeria graminis* f. sp	*TaEDR1*	Immunity regulator	CRISPR-Cas9	Enhanced resistance to disease	Zhang *et al.* (2017)
Wheat	*Triticum aestivum*	*Fusarium graminearum*	*TaLpx-1*	Immunity regulator	CRISPR-Cas9	Enhanced resistance to disease	Wang *et al.* (2018b)
Barley	*Hordeum vulgare* L.	*Wheat dwarf virus* (WDV)	*MP, CP, Rep/ RepA, IR*	Directly targeting the virus genome to develop resistance	CRISPR-Cas9	Directly digesting the virus genome gave asymptomatic plants and no virus presence	Kis *et al.* (2019)

Table 2 continued...

Table 2 continued...

Tobacco	*Nicotiana tabacum*	*Cauliflowe*er musaic virus (CMV)	*ORF1a, ORFCP and 3'-UTR*	Directly targeting the virus genome to develop resistance	CRISPR-Cas9	Suppressed symptom and viral load	Zhang *et al.* (2018b)
Tobacco	*Nicotiana tabacum*	*Turnip mosaic virus (TuMV)*	*GFP, Hc-pro and CP*	Directly targeting the virus genome to develop resistance	CRISPR-Cas13a	Suppressed symptom and viral load	Aman *et al.* (2018)
Potato	*Solanum tuberosum*	*Potato virus X (PVY)*	*P3, CI, NIb and CP*	Targeting the virus genome to develop resistance	CRISPRCas13a	Development of resistance	Zhan *et al.* (2019)
Tomato	*Solanum lycopersicum*	*Pseudomonas syringae*	*SIDMR6–1/cds*	Susceptible gene and facilitate the pathogen's spreading	CRISPR-Cas9	Enhanced diseases resistance against Bacterial speck	De Toledo Thomazella *et al.* (2016)
Tomato	*Solanum lycopersicum*	*Phytophthora capsici*	*SIDMR6–1/cds*	Its paralogue to plants immunity, involve in boosting pathogen growth	CRISPR-Cas9	Enhanced disease resistance	De Toledo Thomazella *et al.* (2016)
Tomato	*Solanum lycopersicum*	*Xanthomonas* spp.	*SIDMR6–1/cds*	Susceptible gene and facilitate the pathogen's spreading	CRISPR-Cas9	Enhanced resistance against Bacterial spot	De Toledo Thomazella *et al.* (2016)
Tomato	*Solanum lycopersicum*	*Oidium neolycopersici* (Powdery Mildew)	*SlMlo1/cds*	SlMlo1 is the susceptible allele for escalating Powdery mildew	CRISPR-Cas9	Enhanced to diseases resistance	Nekrasov *et al.* (2017)
Tomato	*Solanum lycopersicum*	*ToMV and PVX*	*DCL2b*	Targeting the virus genome to develop resistance	CRISPR-Cas9	Suppressed symptom and viral load	Wang *et al.* (2018a)
Tomato	*Solanum lycopersicum*	*Oidium neolycopersici* (Powdery Mildew)	*PMR4/cds*	*PMR4* belongs to Glucansynthase-like (GSL) and act as negative regulator for Salicyclic acid (SA) pathway	CRISPR-Cas9	Enhanced to diseases resistance	Koseoglou (2017)

Table 2 continued...

Table 2 continued...

Tomato	*Solnum lycopersicum*	*Fusarium oxysporum* f.sp. *lycopersici* (*Fusarium* wilt)	*Solyc08g075770/*	Genomic gene is predicted to encode an exopolysaccharide production negative regulator	CRISPR-Cas9	Fusarium wilt resistance	Prihatna *et al.* (2018)
Tomato	*Solanum lycopersicum*	*Botrytis cinerea* (Gray mold)	*SlMAPK3*	Activated protein kinase 3 (*MAPK3*) regulating various pathways	CRISPR-Cas9	Enhanced to diseases resistance	Zhang *et al.* (2018)
Tomato	*Solanum lycoperscum*	*Pseudomonas syringae* pv. *tomato* (Pto) DC3000	*SlJAZ2/cds*	Repressor proteins facilitate COR for interaction by suppressing the JA defense pathway	CRISPR-Cas9	Enhanced disease resistance, defense trade-off solved	Ortigosa *et al.* (2019)
Cucumber	*Cucumis sativus*	*CVYV, PRSV-W and ZYMV*	*eIF4E*	Host factor for RNA viruses	CRISPR-Cas9	Resistance to CVYV, PRSV-W and ZYMV	Chandrasekaran *et al.* (2016)
Cassava	*Manihot esculenta*	*CBSV*	*nCBP1andnCBP-2*	Host factor for RNA viruses	CRISPR-Cas9	Suppressed symptom and viral load	Gomez *et al.* (2019)
Banana	*Musa paradisiaca*	*Gonja Manjaya* (*Musa* spp.)	*eBSV sequence*	Disruption of integrated endogenous banana streak virus (eBSV) in B genome of plantain	CRISPR-Cas9	Resistance developed	Tripathi *et al.* (2019)
Apple	*Malus domestica*	*Erwinia amylovora* (Fire blight)	*DIPM-1 DIPM-2 DIPM-4*	Susceptibility factor/gene play role in fire blight disease	CRISPR-Cas9	Disease resistance not confirmed	Malnoy *et al.* (2016)
Grapes	*Vitis vinifera*	*Erysiphe necator* (Powdery mildew)	*MLO-7*	Susceptibility (S) gene involved in powdery mildew disease	CRISPR-Cas9	Resistance to disease developed	Malnoy *et al.* (2016)
Grapes	*Vitis vinifera*	*Botrytis cinerea* (Gray mold)	*WRKY52*	A transcription factor from WRKY family involved in response to biotic stress	CRISPR-Cas9	Enhanced resistance to disease	Wang *et al.* (2018c)

Table 2 continued...

Table 2 continued...

Grapefruit	*Citrus paradisi*	*Xanthomonas citri* subspecies *citric* (Citrus canker)	*LOB1 (cds/ promoter region)*	Susceptibility (S) gene boosting pathogen growth and pustule development	CRISPR-Cas9	Enhanced resistance to disease	Jia *et al.* (2016; 2017)
Grapefruit	*Citrus sinensis* Osbeck	*Xanthomonas citri* subspecies *citric* (Citrus canker)	*LOB1 (promoter)*	Susceptibility (S) gene boosting pathogen growth and pustule development	CRISPR-Cas9	Enhanced resistance to disease	Peng *et al.* (2017)
Cacao tree	*Theobroma cacao*	*Phytophthora tropicalis* (Black pod disease)	*NPR3*	Immunity regulator	CRISPR-Cas9	Enhanced resistance to disease	Fister *et al.* (2018)

development of climate-resilient crop varieties and the promotion of biodiversity within cropping systems, as highlighted by Eshed *et al*. (2019).

Genome editing techniques offer several advantages compared to other methods, as they allow for the precise modification of specific genes at targeted positions within the genome of commercially cultivated crop varieties (Lowe *et al*., 2016; Debernardi *et al*., 2020; Kevin *et al*., 2022). This means that in a commercial crop variety, the gene of interest, which is associated with a particular trait, can be directly modified (Lowe *et al*., 2016; Debernardi *et al*., 2020; Kevin *et al*., 2022). As a result, there is no longer a need for marker-assisted backcrossing (MABB) to introduce a gene linked to the desired trait from the donor parent. By eliminating the linkage drag, gene editing techniques enable the development of new crop varieties within a shorter time frame of 4-6 years, compared to the 10-12 years required by other crop improvement methods. Additionally, the time taken to eliminate the linkage drag using genome editing techniques is significantly less than that of conventional backcross breeding. This accelerated process would facilitate the availability of genome-edited products in the market (Debernardi *et al*., 2020; Kevin *et al*., 2022). However, the global focus on food security has predominantly centered around staple cereals, often overlooking the importance of perishable crops. These perishable commodities, which include fruits and vegetables, suffer from approximately 33% postharvest losses and waste due to their limited shelf life. It is crucial to recognize that these perishable crops are not only a source of bioactive phytochemicals, but also provide essential nutrients for a healthy lifestyle (Alfa *et al*., 2019; Emma *et al*., 2021). While crop varieties are commonly affected by diseases, insect pests, and environmental stresses, the additional losses incurred through postharvest losses are often disregarded (FAO, 2011; Sawicka, 2019). Fruits and vegetables not only enhance our sensory experiences but also offer a wide range of beneficial nutrients, along with ornamental value. However, their highly perishable nature poses significant challenges. This problem can be solved by using gene editing techniques for the improvement and development of new varieties with enhanced shelf life that ultimately reduces the postharvest losses (Emma *et al*., 2021).

The market for genome editing is categorized into three main sectors: research, agricultural and industrial, and human therapeutics biotechnologies (Brinegara *et al*., 2017). Among these sectors, research holds the largest market share, accounting for 38.6%. One of the key reasons for this dominance is the superiority of

Table 3 : Genome editing techniques used for development of genome-edited products with improved quality.

Crop	Botanical name	Targeted gene	Gene function	Genome editing tool	Outcome	Reference
Rice	*Oryza sativa*	Phytoene desaturase *CrtI* and maize Phytoene synthase *(PSY)* genes	Enhances beta-carotene and vitamin A content	CRISPR-Cas9	Beta-carotene and vitamin A content increased	Dong *et al*. (2020)
Rice	*Oryza sativa*	Fatty acid desaturase (*OsFAD2-1*)	Targeted mutagenesis in the OsFAD2-1 gene for producing high oleic/low linoleic in rice bran oil (RBO)	CRISPR-Cas9	Enhanced oleic/low linoleic in rice bran oil (RBO)	Abe *et al*. (2018)
Rice	*Oryza sativa*	*GW2*	Negative regulator for grain length and width	CRISPR-Cas9	Enhanced grain length and width	Achary and Reddy (2021)
Rice	*Oryza sativa*	*OsSPL16/qGW8*	Negative regulator for the grain size	CRISPR-Cas9	Improved grain size	Usman *et al*. (2021)
Rice	*Oryza sativa*	Glutamate decarboxylase 3 (*OsGAD3*)	Trimming the coding region of the CaMBD domain from the OsGAD3 gene produces higher gamma-aminobutyric acid (GABA) content	CRISPR-Cas9	Enhances higher gamma-aminobutyric acid (GABA) content	Akama *et al*. (2020)
Rice	*Oryza sativa*	*OsBADH2*	Creation of novel alleles of *OsBADH2*, leading to the introduction of aroma into an elite non-aromatic rice variety ASD16	CRISPR-Cas9	Aroma introduced in rice variety ASD16	Ashokkumar *et al*. (2020)
Rice	*Oryza sativa*	Betaine aldehyde dehydrogenase 2 (*OsBADH2*)	Loss of function (*OsBADH2*) affects the biosynthesis of 2-acetyl1-pyrroline (2-AP), which is responsible for the aroma in fragrant rice	CRISPR-Cas9	Enhanced aroma in fragrant rice	Hui *et al*. (2022)
Rice	*Oryza sativa*	*OsGBSSI* (granule-bound starch synthase I) or waxy (*Wx*) gene	Downregulation of *Wx* expression associated with fine-tuning grain amylose content	CRISPR-Cas9	Increased amylose content	Huang *et al*. (2020)
Rice	*Oryza sativa*	*OsNRAMP2*	Remobilization and distribution of Fe and Cd	CRISPR-Cas9	Remobilized Fe and Cd	Chang *et al*. (2022)
Maize	*Zea mays*	*CLE*	Engineered CLE genes are used to increase the yield	CRISPR-Cas9	Enhanced yield	Liu L. *et al*. (2021)

Table 3 continued...

Table 3 continued...

Maize	*Zea mays*	*ZmBADH2a* and *ZmBADH2b*	Enhances popcorn-like scent in seeds from the double mutant	CRISPR-Cas9	Popcorn-like scent in seeds	Wang *et al*. (2021)
Peanut	*Arachis hypogaea*	*FAD2A* and *FAD2B* knock down of genes *FAD2A* and *FAD2B*	Control the oleic acid content	CRISPR-Cas9	Increased oleic acid content	Yuan *et al*. (2019)
Rapeseed	*Brassica napus*	*SFAR4* and *SEARS*	Control oleic acid linoleic and linolenic acid contents	CRISPR-Cas9	Increased oleic acid content and decreased linoleic and linolenic acid contents	Karunarathna *et al*. (2020)
Rapeseed	*Brassica napus*	*BnITPK*	Phytic acid content	CRISPR-Cas9	Knockdown decreased the Phytic acid content	Sashidhar *et al*. (2020)
Eggplant	*Solanum melongena*	*PP04, PPOS* and *PP06*	Knock down of *PP04, PPOS* and *PP06* decreased browning	CRISPR-Cas9	Decreased the browning	Maioli *et al*. (2020)
Potato	*Solanum tuberosum*	Polyphenol Oxidases (*stPPO2*)	Knockdown of the *stPPO2* reduced the browning of the tuber	CRISPR-Cas9	Reduced the browning of the tuber	González *et al*. (2020)
Tomato	*Solanum lycopersicum*	*SlDDB1, SlDET1, SlCYC-B*	Upregulation of *SlDDB1, SlDET1* and *SlCYC-B* increased carotenoid, lycopene and β carotene	CBE	Increased carotenoid, lycopene, and β carotene	Hunziker *et al*. (2020)
Tomato	*Solanum lycopersicum*	Salt-tolerant *SlHKT1*	Salt tolerance	CRISPR/ LbCpf1	Enhanced salt tolerance	Vu *et al*. (2020)
Tomato	*Solanum lycopersicum*	*SlINVINH1* and *SlVPE5*	Knock down of genes (*SlINVINH1* and *SlVPE5*) increased glucose, fructose and total soluble solids (TSS)	CRISPR-Cas9	Increased glucose, fructose and total soluble solids (TSS)	Wang *et al*. (2021a)
Camelina	*Camelina sativa*	*CsFAD2*	Knock down of *CsFAD* increased oleic acid contents	CRISPR-Cas9	Increased oleic acid contents	Lee *et al*. (2021)
Banana	*Musa paradisiaca*	*MaACO1*	Knock down of *MaACO1* increased shelf life	CRISPR-Cas9	Increased shelf life	Hu *et al*. (2021)

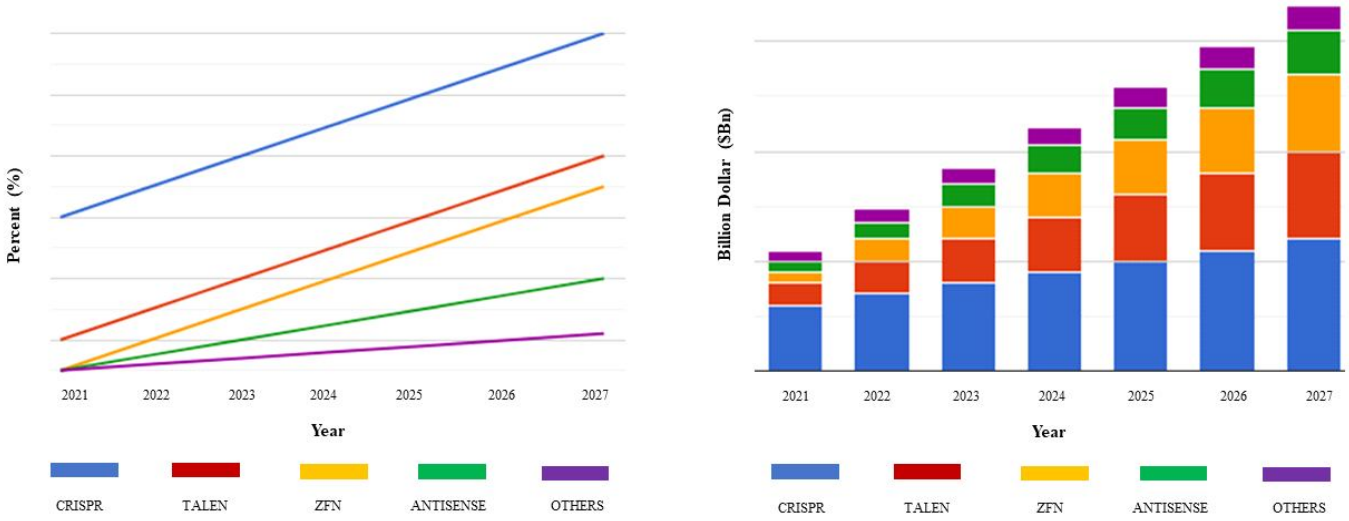

Fig. 2 : Recent developments in the global market of various genome editing tools (Source: https://www.skyquestt.com/services/Data-Analytics-Services).

CRISPR-Cas technology over other gene editing techniques, as it overcomes the limitations associated with pre-existing gene-editing technologies. Companies acquire CRISPR-Cas licenses to distribute reagents related to gene editing biotechnology research in academic, research, and other institutional settings (Gupta and Musunuru, 2014). Approximately 25% of these companies are dedicated to utilizing gene editing technologies in agricultural biotechnology, specifically in the modification of plants and animals, which has the potential to enhance sustainable food production. Furthermore, the less stringent regulatory standards for gene edited products have facilitated the commercialization of genome edited food products (Wolt *et al*., 2016).

Genome editing technology is not a cure-all solution; however, it is widely accepted and accessible, with significant market potential that can democratize the benefits of modern science. Various gene editing tools, such as CRISPR-Cas, TALEN, ZFN, antisense and others, hold immense promise in the global market (https://www.skyquestt.com/services/Data-Analytics-Services) (Fig. 2). In 2022, the market for reagents, chemicals and glassware related to gene editing technology (CRISPR, TALEN, and ZFN), including different types of enzymes (nucleases), gRNA, biolistic or agrobacterium methods, etc., reached USD 3.3 billion in agriculture and human health. It is expected that this technology will continue to dominate the world market in the coming years (https://www.marketsandmarkets.com). The CRISPR-Cas technique is cost-effective and can be applied to both major and minor crops, including orphan crops, to enhance agricultural diversity (Lemmon *et al*., 2018; Kevin *et al*., 2022). Globally, this technology has been employed in over 40 crops to improve agronomic traits, food and feed quality, and develop climate-resilient crops (Menz *et al*., 2020). The acceptance of gene editing technology varies among countries and depends on the decisions made by policymakers, the scientific community, regulatory authorities, and society as a whole (Schmidt *et al*., 2020). Genome editing technology has already demonstrated successful trait improvements in various crops, such as heat tolerance and apomixis in potatoes, reduced glycaemic index and apomixis in rice, reduced acrylamide, phytate and polyphenol oxidase in wheat, enhanced nutritional quality and digestibility in beans, low phytate and high provitamin A in maize, striga resistance in sorghum, reduced aflatoxin in groundnut, delayed flour rancidity in pearl millet, and brown streak virus resistance and haploid induction in cassava (Kevin *et al*., 2022). Recently, the Meeting of Agricultural Chief Scientists of G20 (MACS) also emphasised the potential use of genome editing technology for sustainability development to secure food security, particularly in middle-and low-income countries (Kevin *et al*., 2022).

Limitations of Gene Editing Techniques

Gene editing techniques, such as CRISPR/Cas, have inherent limitations when applied to crops. The process relies on genome sequencing to generate gRNA and without a available or assembled genome sequence, it becomes impossible to identify potential targets for editing. Additionally, the design of complementary gRNA sequences, necessary for directing Cas nucleases to the target site, is also hindered by the absence of a gene sequence of interest. Another concern in gene editing is the off-target activity of CRISPR/Cas, which poses a significant challenge. Furthermore, the requirement for a

PAM sequence restricts gene editing in certain areas of the genome, limiting the scope of CRISPR/Cas base editing. Base editing also faces limitations in making specific nucleotide changes. However, prime editing offers a potential solution by enabling highly targetable "find and replace" edits. Moreover, crops derived from knock-in editing are classified as genetically modified (GM) crops and must comply with local and international regulatory policies. Gene editing provides an opportunity to address the widespread societal distrust of transgenic crops and the burdensome regulations and global agricultural disparities associated with them. To overcome the current limitations of gene editing, extensive basic research is necessary. Additionally, the transformation and regeneration processes are expected to remain significant bottlenecks in crop gene editing for the foreseeable future. Therefore, it is crucial to focus on expanding genomic resources and developing improved protocols for different crop gene editing and transformation. These efforts will ensure the rapid advancement of agronomically important crops through gene editing (Matthew and Krainer, 2021).

Challenges in Genome Editing Technology

The agricultural revolution driven by gene editing faces numerous challenges, including the occurrence of off-target effects in the editing techniques, the efficient delivery of CRISPR-Cas payloads and the complex legal and regulatory frameworks surrounding genome-edited crops. In the realm of genome editing techniques, particularly the CRISPR/Cas9 system, scientists are primarily concerned with the off-target effects. This technology induces double-stranded breaks through the Cas9 enzyme, and when Cas9 acts on unintended sites, it leads to undesired mutations. While CRISPR/Cas9 technology can tolerate a few mismatches (1-3) in its intended target site, the occurrence of more than 50% mutations or off-target effects at sites other than the intended targets remains a significant concern.

The availability of gene-edited products in the market is a result of their transition from being confined to research laboratories. This transition has been made possible by the modification of regulations in numerous countries. The commercialization of new technologies also heavily relies on consumer preference and satisfaction. However, the acceptance of genetically modified (GM) crops/products varies across different countries. Some countries still associate genome edited crops/products with GM products, which raises significant concerns (Chen and Gao, 2020). It is crucial to educate and inform consumers about the benefits of this novel technology and emphasize that it should not be equated with GM products. While the regulations for genome editing differ among countries, policymakers should establish regulations that are distinct from those governing GM products and are acceptable globally (He and Krainer, 2021). However, certain countries consider these regulations to be equivalent to those for GM crop varieties/products (Hundleby and Harwood, 2022). As genome editing technologies and crops/products continue to advance rapidly with enhanced precision and efficiency, regulations should be developed in alignment with those for products developed through conventional breeding methods (Menz *et al*., 2020). In this context, regulations should not only be based on scientific evidence but also take into account public opinion and satisfaction. Furthermore, the acceptance of market-based genome edited products heavily relies on consumer awareness and opinion, as many private companies solely focus on developing such products (Sprink *et al*., 2016; Ishii and Araki, 2017).

In addition to these challenges, the lack of infrastructure poses a significant obstacle for genome editing research in developing and underdeveloped countries. Research and academic laboratories in these regions require access to genome editing facilities, which necessitates capital investments. The high cost of genome editing equipment, shortage of trained personnel, and complex regulations further hinder small laboratories and pharmaceutical firms from initiating gene editing research. Moreover, the research and academic institutions that carry out basic research find it difficult to start the research on genome editing due to funds constraints (FAO, 2022).

Future Perspectives

The CRISPR-Cas system, a gene editing technique, offers a cost-effective, convenient and efficient tool for modifying major crops to enhance their tolerance to biotic and abiotic stresses and improve the quality of food products. One of the advantages of this technique is the reduced regulatory restrictions since it does not involve the insertion of foreign DNA. Additionally, the products derived from gene editing technology are readily accepted by society. Initially, CRISPR technology was primarily used to modify a single gene for crop improvement. However, it has the potential to manipulate multiple genes simultaneously by incorporating multiple sgRNA expression cassettes in a single CRISPR vector or by increasing RNA production through an endogenous RNA processing system. In the future, advanced tools like "Base-editor," "Prime-editors" and "Express Edit" can further enhance gene editing and delivery systems,

enabling more efficient modifications of target genes. These techniques, including gene editing have significantly increased crop productivity, regardless of regulatory constraints and have satisfied consumer demands. The improved food productivity can be attributed to the utilization of advanced techniques in plant breeding. However, when advanced technologies are applied within conventional systems, concerns arise regarding modifications made during crop development, which may affect consumer acceptance. Therefore, genome editing techniques, particularly CRISPR/Cas9, should be permitted for the development of market-oriented products. These techniques enable the creation of crop varieties and products with greater efficiency and precision, addressing the food requirements of developing and underdeveloped countries. Furthermore, this approach contributes to achieving the United Nations' Sustainable Development Goal of "ending hunger by 2030" by enhancing food production (Venezia and Krainer, 2021).

The progress in genome editing technologies, such as CRISPR/Cas, ZFNs and TALENs, has facilitated the development of convenient and cost-effective techniques. The adoption of these gene editing technologies has resulted in a significant growth in the engineering market, reaching approximately 50% by 2022 (FAO, 2022). This growth can be attributed not only to the sale of genetically modified crops and products, but also to the increased demand for consumable plasticware and expensive reagents. Additionally, the successful development and global market penetration of genome editing crops and products heavily rely on active collaboration and communication between the government and various stakeholders. It is crucial for public sectors and government organizations to safeguard the interests and benefits of all stakeholders while implementing a rational regulatory system. The utilization of CRISPR-based agricultural gene editing holds immense potential for the future of agriculture-based products. This technique allows for the design of genes that enhance crop quality, production, and vitamin synthesis. Furthermore, CRISPR-based gene editing has the potential to contribute significantly to achieving the 2030 goal of eradicating all forms of human malnutrition, hunger and food insecurity.

Author contributions

RKS conceived the review. PJ wrote a draft of the manuscript and prepared the figure and table. RKS, PJ and BSC edited and finalized the manuscript. All authors read and approved the ûnal manuscript.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

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