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RAO conceptualize the work. RAO and JTO collated the resources and other materials for the work. The three authors contributed to the writing of the manuscript. ATO edited the manuscript while RAO further carried out visualization and referencing formatting of the work

REVIEW

Applications of Clustered Regularly Interspaced Short Palindromic Repeats in Food Security and Nutraceuticals

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Abstract

The CRISPR/Cas9 system is a revolutionary genome-editing tool that enables precise and inheritable modifications, transforming plant genetic engineering. Previous literature has indicated that, in agriculture, CRISPR has improved crop yield, biofortification, and resistance to environmental stressors, fostering resilient and high-yielding crops essential for sustaining a growing global population. In nutraceuticals, CRISPR has enhanced the biosynthesis of bioactive compounds such as anthocyanins, flavonoids, and omega-3 fatty acids, improving the nutritional and therapeutic value of crops.

Despite its immense potential, CRISPR technology faces technical, ethical, and regulatory challenges, including off-target effects, accessibility concerns, and public acceptance. Addressing these issues is crucial for its sustainable adoption. Future innovations, including the integration of CRISPR with complementary technologies, will further improve its precision and accessibility, which will facilitate advancements in food security and in the nutraceutical industry. This review aims to explore the applications of CRISPR in enhancing food security and nutraceutical development, assess its impact on crop improvement, and discuss the challenges associated with its adoption.

Keywords: CRISPR, Gene editing, Food security, Nutraceuticals, Biofortification, Agricultural biotechnology

1. Introduction

Global food security remains a critical issue as the global population continues to grow. The population of the globe is increasing at an annual rate of 1.1 % [1]. This implies that the rate of food consumption is also rising, ultimately leading to a concurrent rise in food scarcity and insecurity. It has been reported that the number of people experiencing acute food insecurity increased from approximately 600 million in pre-COVID-19 pandemic years to about 702−828 million people in 2021 (an increase of about 150 million people) [2]. To meet the needs of a projected population of 9.7 billion by 2050 [3], food production must rise by at least 70 % globally [4]. However, this target is threatened by environmental challenges. Climate change significantly undermines agricultural productivity, with heat stress (one of the most significant abiotic stressors) alone reducing wheat yields by 6 % per degree Celsius rise in temperature [5]. This impact is further exacerbated in regions like South Asia, where grain yield losses during grain-filling stages range from 6 to 10 % per degree increase [6]. Additionally, erratic rainfall and depleting groundwater are reducing cultivable land, particularly in vulnerable regions like Sub-Saharan Africa and South Asia [7]. Fertilizer management is another challenge. Despite nitrogen fertilization contributing to 40−64 % yield increases in temperate climates, its overuse in some areas causes environmental pollution, while underuse in others limits productivity [8,9]. Also, phosphorus which is essential for crop growth faces global supply challenges because most of the mineable phosphorus reserves are concentrated in a few

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countries including Morocco (85 %) and some countries in eastern Asia [10]. This has left 30 % of global croplands phosphorus-deficient, severely affecting low-income nations in Latin America, Central Asia and sub-Saharan Africa [11].

The demand for nutraceuticals has surged globally, driven by an increasing emphasis on preventive healthcare and natural wellness solutions. Projections estimate the global nutraceutical market to reach $722.49 billion by 2027, growing at a compound annual growth rate (CAGR) of 8.3 % from 2020 to 2027 [12]. This growth is fueled by the steadily rising global population and persistent food insecurity. As available food systems struggle to meet nutritional needs, nutraceuticals offer a viable solution by providing health benefits beyond basic nutrition [13]. Another factor contributing to the increase in demand for nutraceuticals is the rising cost of healthcare [14]. This has prompted a shift toward cost-effective alternatives like nutraceuticals.

Given these global challenges, there is an urgent need for innovative solutions to enhance both food production and nutritional quality [4,12]. Food security and nutraceuticals are particularly relevant focal points because they represent two critical aspects of global health and sustainability. Ensuring food security goes beyond increasing agricultural yields; it requires the development of resilient, nutrient-dense crops that can withstand environmental stressors while meeting dietary needs [4]. On the other hand, nutraceuticals offer an opportunity to combat malnutrition and lifestyle-related diseases by fortifying diets with bioactive compounds that provide additional health benefits [14]. With its precision and versatility, CRISPR technology holds immense potential to address these interrelated challenges [15].

Clustered regularly interspaced short palindromic repeats (CRISPR) has emerged as a revolutionary genome-editing tool, transforming agriculture and nutrition through precise genetic modifications. Unlike traditional methods such as transgenics, CRISPR enables targeted and inheritable genome changes without introducing foreign DNA, minimizing ethical and environmental concerns [15]. The technology is simple, cost-effective, and highly reproducible, making it ideal for addressing global challenges such as malnutrition and food insecurity [16]. CRISPR has been extensively employed in crop biofortification programs, enhancing the nutritional profiles of cereals like rice and wheat and vegetable crops like tomatoes and potatoes. This includes increasing vital nutrients such as iron, zinc, and vitamin A while improving crop resistance to environmental stresses like drought and pests [17]. CRISPR is versatile in that it can be used to tailor crops for enhanced shelf life, aroma, and flavor [18]. By addressing the challenges of nutritional deficiencies and sustainable food production, CRISPR can serve as a useful tool in the pursuit of global food security and nutrition. The present review discusses the application of CRISPR gene editing in the enhancement of food security and the development of nutraceuticals.

2. Mechanism of CRISPR/Cas9 gene editing

The CRISPR-Cas system is an adaptive defense mechanism found in most archaebacteria, which helps protect them from foreign genetic material, including viruses and bacteriophages [19]. The CRISPR/Cas9 (CRISPR-associated protein 9) system consists primarily of two components: the Cas9 nuclease, which acts as molecular scissors, and a single-guide RNA (sgRNA), which directs Cas9 to the target DNA sequence. The sgRNA is a fusion of CRISPR RNA (crRNA) and *trans*-activating CRISPR RNA (tracrRNA). The crRNA contains a sequence complementary to the target DNA, while the tracrRNA binds to the Cas9 protein, forming a complex. Cas9 identifies the target site by recognizing a short DNA motif known as the protospacer adjacent motif (PAM) near the target sequence. Once bound, Cas9 induces a double-strand break (DSB) in the DNA [20]. Recent advancements have led to the development of high-fidelity Cas9 variants, such as SpCas9-HF1 and eSpCas9, which exhibit reduced off-target activity, improving the precision and reliability of gene editing. Additionally, engineered Cas enzymes like Cas12 and Cas13 have expanded the scope of CRISPR applications, with Cas12 targeting DNA using different PAM requirements and Cas13 enabling RNA editing for transcriptome modifications [21].

The resulting DSB is repaired by the cell's endogenous DNA repair mechanisms. Non-homologous end joining (NHEJ) introduces small insertions or deletions at the break site, often leading to gene disruption. Alternatively, homology-directed repair (HDR) incorporates a donor DNA template to introduce precise genetic modifications [20]. However, since HDR efficiency is typically low, recent advancements have focused on increasing its effectiveness to optimize precise gene insertion for therapeutic and agricultural applications. Strategies include the use of HDR enhancers, cell cycle modulation to favor the S/G2 phase, and the incorporation of chemically modified donor DNA templates [20,21].

Traditional CRISPR editing relies on double-strand breaks (DSBs), but there are newer approaches with improved precision and efficiency. Base editing allows for the direct conversion of one DNA base to another without inducing DSBs, reducing errors and improving safety. This method involves cytosine base editors (CBEs) and adenine base editors (ABEs), which chemically modify specific nucleotides. Furthermore, prime editing offers an even more flexible tool by inserting or deleting small DNA sequences in a programmable manner, expanding the range of possible genetic modifications [21].

The schematic illustration for the mechanism of the CRISPR/Cas9 genome editing system is depicted in Fig. 1.

3. CRISPR in food security

One of the most significant applications of CRISPR in agriculture is the enhancement of crop yield. Studies have shown the potential of CRISPR to address global food demands by increasing the productivity of staple crops (Fig. 2). The grain number 1a (Gn1a) and grain size 3 (GS3) genes in rice were edited to improve both grain number and size, resulting in higher overall yields [22]. Similarly, modifications to the OsSPL16 gene in rice were shown to improve grain quality and increase overall production [23]. In wheat, CRISPR/Cas9 (CRISPS associated protein 9) was used to target the TaSBEIIa gene, resulting in high amylose content and improved starch composition. This innovation not only increased yield but also enhanced nutritional quality to address dietary fiber deficiencies [24]. Furthermore, mutations in photosynthesis-related genes have shown potential for increasing biomass and seed production in maize and sorghum which can help to meet food demands in low-resource environments [25].

Abiotic stresses, such as drought, salinity, and extreme temperatures, significantly limit agricultural productivity. CRISPR has been used to develop stress-tolerant crop varieties by editing genes responsible for stress responses. For example, the OsNRT1.1A gene in rice was modified to enhance nitrogen use efficiency, allowing plants to thrive in nitrogen-poor soils [26]. Similarly, editing genes

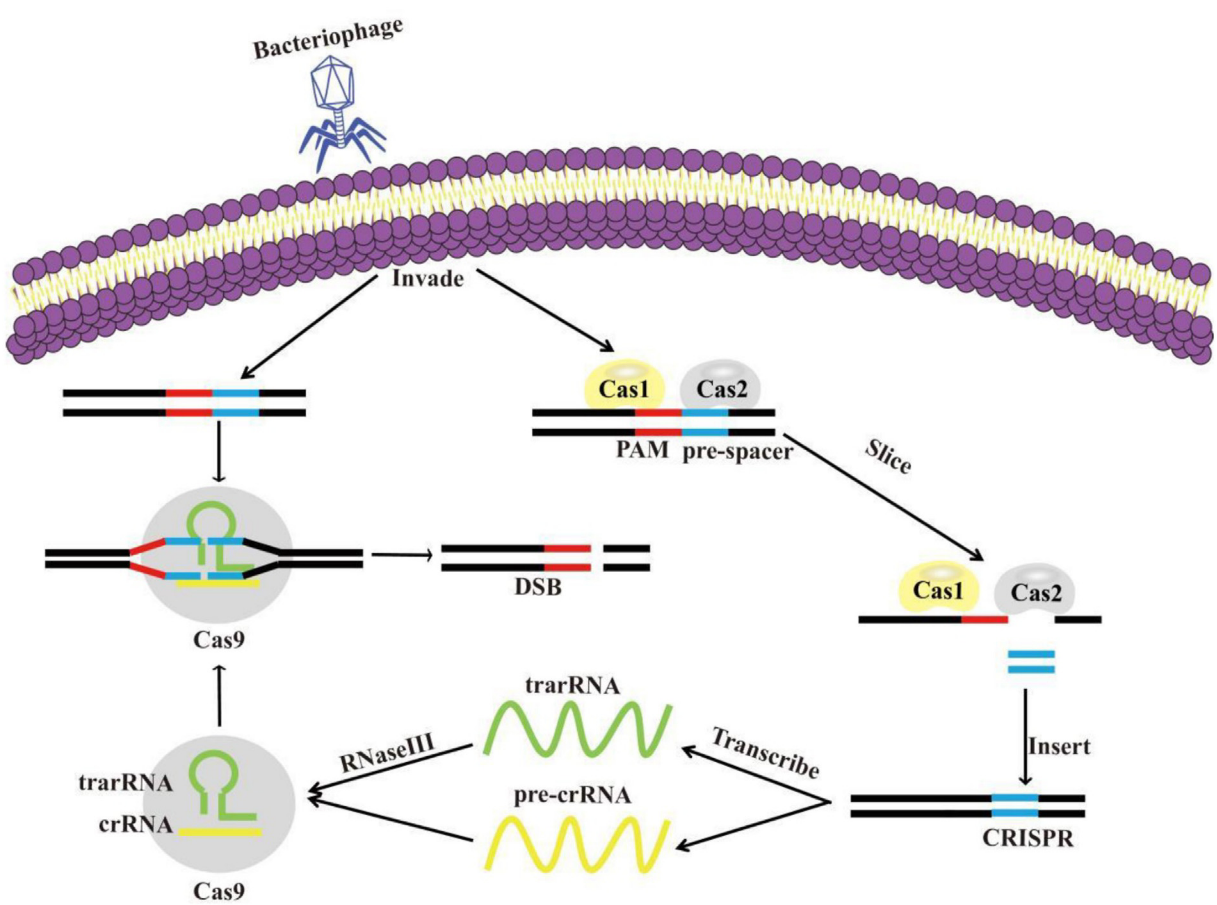

Fig. 1. A schematic representation of the. CRISPR/Cas9 gene editing mechanism. Adapted from Jiang et al. *[21].*

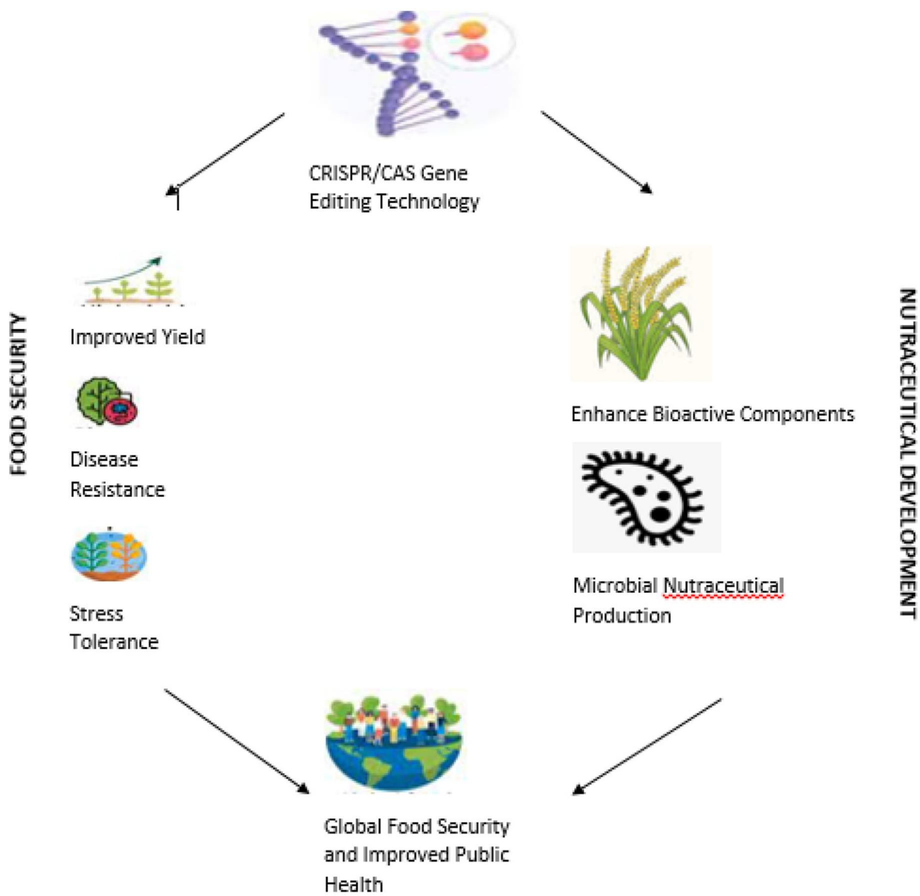

Fig. 2. An overview of the role of CRISPR technology in food security and nutraceutical development.

encoding heat shock proteins improved thermal tolerance in crops like barley and wheat [27]. The OsPYL1 gene in rice plays a role in abscisic acid signaling, which is a pathway critical for water stress response. A study showed that targeting this gene can lead to improved drought tolerance in rice [28]. This advancement is particularly important for regions experiencing irregular rainfall and water scarcity. Moreover, CRISPR-enabled alterations to the OsDT11 gene have enhanced drought resistance and reduced water consumption in rice plants, providing a sustainable solution to water management in agriculture [29].

Another factor promoting food insecurity is prevalence of pests and pathogens, which cause significant crop losses worldwide, and this has necessitated the development of resistant crop varieties. CRISPR has facilitated the removal of susceptibility genes to enhance resistance. For instance, editing the mildew resistance locus O (MLO) gene in barley conferred broad-spectrum resistance to powdery mildew, a major fungal disease. This technique has been widely adopted due to its effectiveness and the reduced need for chemical fungicides [30]. In rice, bacterial blight resistance was improved by editing the Xa23 gene, a major resistance determinant [31]. Similarly, viral resistance in cassava was achieved by targeting the coat protein gene of the African cassava mosaic virus using CRISPR/Cas9 [32]. These innovations reduce dependency on chemical pesticides and promote sustainable agricultural practices.

Erratic weather patterns and climate variability are also some of the factors affecting food security, and therefore, crops need to adapt to them. CRISPR has enabled the rapid development of short-duration crop varieties that complete their life cycles before adverse weather conditions set in. For example, early-maturing rice varieties were engineered by editing the Hd1 and Hd3a genes, ensuring stable yields in regions with short growing seasons [33]. Combining CRISPR with speed breeding (a technique that shortens the time it takes to breed crops by manipulating the environmental conditions in which they are grown) has further accelerated the development of climate-resilient crops. This approach has been applied to wheat and barley to enhance their adaptability to fluctuating temperatures and reduced water availability [34,35].

These advancements are particularly significant for regions most vulnerable to climate change, such as sub-Saharan Africa and South Asia.

CRISPR has also targeted genes involved in nutrient uptake and metabolism to optimize fertilizer use efficiency. In maize, modifications to nitrate transporter genes improved nitrogen use efficiency, reducing the environmental impact of excessive fertilizer application [36,37]. Likewise, editing the phosphorus transporter genes in rice enhanced phosphorus uptake from the soil to ensure maximum and efficient utilization of the available phosphorus [38,39].

Moreover, the integration of CRISPR with nanotechnology has enhanced the precision and efficiency of genome editing. Nanoparticles are increasingly being used to deliver CRISPR components into plant cells so as to minimize off-target effects and ensure targeted gene editing. This approach has been particularly effective in developing disease-resistant and high-yielding crops [40]. For example, in wheat, CRISPR-loaded nanoparticles were successfully used to edit to multiple genes associated with disease resistance and stress tolerance [41].

Additionally, CRISPR has been employed to enhance the quality and shelf life of crops. In tomatoes, targeted mutations in the SP5G gene accelerated flowering and fruiting, enabling earlier harvests [42,43]. In potatoes, the GBSS gene was edited to increase amylopectin content, improving starch properties for industrial applications [44]. Similar approaches have been used in oilseed crops like *Camelina sativa* and *Brassica napus* to improve oil quality by increasing oleic acid content, which will ensure it can be stored for longer [45–47].

Some of these applications of CRISPR in enhancing crop yield and resistance and other applications have been summarized in Table 1.

4. CRISPR in nutraceutical development

CRISPR has been instrumental in addressing micronutrient deficiencies through the biofortification of staple crops (Fig. 2). Based on research conducted across multiple studies, Majumder *et al.* [48] highlighted that biofortification of rice with iron and zinc by targeting transporter genes enhances the nutritional value of this global staple, thereby helping in combating "hidden hunger." Similarly, Liang *et al.* [49] reported that CRISPR was used to edit the ZmIPK1A and ZmMRP4 genes in maize so as to reduce phytic acid production. Phytic acid binds essential minerals, such as calcium, zinc, and iron, and inhibits their absorption in humans [50]. By reducing its levels, CRISPR can enhance the bioavailability of these nutrients. Anthocyanin-enriched crops are another example of CRISPR-based biofortification. Zhang *et al.* [51] showed that crossing the transgenic orange SlE8:AtMYB12 tomato line with the purple anthocyanin-enriched AmDel/AmRos1 tomato line resulted in almost 100 % increase in anthocyanin levels in the new hybrid tomato compared to the

Table 1. A list of applications of CRISPR/Cas9 technology in improving food security.

Plant	Gene Edited	Result	Reference
Rice	Gn1a, GS3	Increased grain number and size	[22]
Rice	OsSPL16	Improved grain yield and quality	[23]
Wheat	TasBeIIa	High amylose content, improved starch composition	[24]
Rice	OsNRT1.1A	Improved nitrogen use efficiency	[26]
Rice	OsPYL1, OsDT11	Improved drought tolerance	[28,29]
Barley	MLO	Resistance to powdery mildew	[30]
Rice	Xa23	Resistance top bacterial blight	[31]
Cassava	Coat protein gene of African cassava mosaic virus	Resistance to viral infections	[32]
Tomato	SP5G	Early flowering	[42,43]
Potato	GBSS	Increased amylopectin content	[44]
Rice	OsGL3.1	Increased grain size and yield	[75]
Wheat	TaCKX2-D1, TaGW2	Increased grain yield and kernel weight	[76]
Maize	ZmALS1, ZmALS2	Improved herbicide tolerance	[77]
Barley	HvPM19	Reduced grain dormancy, improved malting quality	[78]
Camelina	FAD2	Increased oleic acid content for improved oil quality	[79]
Soybean	GmFT2a	Delayed flowering time	[80]
Tomato	GGPPS, ZISO, DXS, G3P, PDS	Increased lycopene content	[81]
Rice	OsLOGL5	Increased root growth and tiller number	[82]
Wheat	TaDEP1, TaGASR7	Improved plant architecture for better yield	[76]
Oilseed Rape	ALS1	Improved herbicide resistance	[83]
Watermelon	CLBG1	Reduced seed size, improved germination	[84]

purple AmDel/AmRos1 tomato. Anthocyanins are potent antioxidants associated with reduced risks of chronic diseases, including cardiovascular and neurodegenerative disorders. Potatoes have also been engineered to lower glycoalkaloid levels, enhancing safety and nutritional quality [52]. All these CRISPR-based modifications help supply essential micronutrients that the body would have otherwise been deprived of [48].

Secondary metabolites, such as carotenoids, flavonoids, phenolics, and alkaloids, are critical components of nutraceuticals due to their therapeutic properties. CRISPR has been extensively applied to increase the production of these metabolites in food crops. Singh *et al.* [53] summarized that carotenoid biosynthesis pathways in crops like rice, maize, and tomatoes have been optimized by editing key regulatory genes such as LCY-B1, LCY-B2, and PSY, leading to increased beta-carotene content. This improvement directly addresses vitamin A deficiency, a major cause of blindness and mortality in children worldwide. In another study according to Singh *et al.* [53] found that the modification of MYB and Aft transcription factors in purple tomatoes and red cabbage has significantly increased flavonoid concentrations, yielding crops with enhanced nutraceutical potential. CRISPR has been used to improve the nutritional profiles of underutilized legumes such as *Prosopis cineraria*, *Acacia senegal*, and *Cyamopsis tetragonoloba* (guar), which are rich in proteins, flavonoids, and phenolics. By selectively knocking off genes associated with undesirable traits, such as off-flavors and anti-nutritional factors, these crops have been transformed into viable sources of functional foods. In guar, for instance, the removal of genes responsible for its "beany" flavor has enhanced its palatability, while increasing its protein content through the modification of storage protein genes [54].

Omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA), are essential for cardiovascular and neurological health. These compounds are now being produced in oilseed crops through CRISPR-based genetic modifications, as opposed to being obtained from fish oil. For instance, by targeting fatty acid desaturase genes in *Camelina sativa*, researchers have developed crop varieties with higher omega-3 fatty acid content [55,56]. This innovation offers a sustainable and plant-based source of these critical nutrients, reducing reliance on overfished marine resources.

CRISPR has been pivotal in developing functional foods that provide additional health benefits. As mentioned earlier, high-fiber wheat varieties, for example, have been engineered by editing the TaSBEIIa gene, leading to increased resistant starch levels [24]. Resistant starch acts as a prebiotic, promoting gut health and reducing the risk of colorectal cancer [57]. Also, it has been reported that the editing of FAD2 and GmSWEET genes in soybeans resulted in increased oleic acid content, producing oils with better cooking properties and enhanced cardiovascular benefits [58].

CRISPR has also been applied to optimize microbial cell factories for the production of high-value nutraceuticals. Microorganisms such as *Saccharomyces cerevisiae* and *Escherichia coli* have been engineered to produce polyphenols, flavonoids, and omega-3 fatty acids with high efficiency. For example, CRISPR was used to enhance the metabolic pathways of these microbes, resulting in increased yields of resveratrol and naringenin, which have antioxidant and anti-inflammatory properties [59−61]. In addition to optimizing metabolic pathways, CRISPR has enabled the multiplex editing of genes in microbial systems, allowing for the simultaneous production of multiple nutraceutical compounds. This approach reduces production costs and increases scalability, making microbial cell factories an attractive alternative for nutraceutical production [62].

These applications of CRISPR in the development of nutraceuticals have been summarized in Table 2.

5. Challenges and ethical considerations

A major technical limitation of CRISPR technology is off-target effects, where unintended genetic modifications occur. These off-target edits can lead to unpredictable mutations, some of which may be detrimental to the organism or its environment. This issue is particularly concerning in crops, where unintended edits could reduce yield, nutritional quality, or environmental adaptability [63]. Although advances such as high-fidelity CRISPR variants (e.g., SpCas9-HF1 and eSpCas9) and artificial intelligence-driven predictive algorithms have been developed to improve targeting accuracy [64], complete elimination of off-target mutations remains a challenge. Continued research on alternative genome-editing tools, such as prime editing and base editing, which do not require double-strand breaks, could further mitigate this challenge [21].

Additionally, efficient delivery of CRISPR components into plant cells remains a significant hurdle. Current methods, including biolistic delivery and Agrobacterium-mediated transformation, are often inefficient, costly, or limited to specific plant species [65]. Additionally, these techniques may result in mosaicism, where only some cells in an organism

Table 2. A list of applications of CRISPR/Cas9 technology in nutraceutical development.

Plant	Gene Edited	Result	Reference
Rice	OsNAS1, OsNAS2	Increased iron and zinc content (biofortification)	[48]
Maize	ZmIPK1A, ZmMRP4	Reduced phytic acid, enhancing mineral bioavailability	[49]
Tomato	MYB, Aft	Increased anthocyanin content, enhancing antioxidant properties	[51]
Potato	StSSR1	Reduced glycoalkaloid levels, improving food safety	[52]
Soybean	FAD2, GmSWEET	Increased oleic acid, improving oil quality	[58]
Camelina	FAD3	Increased omega-3 fatty acid content for cardiovascular health	[55,56]
Yeast (*Saccharomyces cerevisiae*)	Various metabolic pathway genes	Enhanced production of polyphenols and flavonoids for nutraceutical use	[59]
Escherichia coli	Resveratrol biosynthesis genes	Increased resveratrol yield with antioxidant benefits	[60]

are edited, reducing consistency and reliability in agricultural applications [66]. Recent developments in nanoparticle-based CRISPR delivery and viral vectors have shown potential, but large-scale implementation remains limited by cost and regulatory constraints. Future improvements in non-GMO delivery methods, such as ribonucleoprotein (RNP) delivery, may provide a pathway for broader adoption [67].

Also, navigating the regulatory landscape for CRISPR-edited crops is complex and varies widely across regions. In the European Union, for example, CRISPR-edited organisms are classified as genetically modified organisms (GMOs), requiring stringent regulatory approval. Conversely, countries like the United States consider CRISPR-edited crops non-GMO if no foreign DNA is introduced. This inconsistency in global regulations presents a major hurdle in international (cross-border) CRISPR research [68,69]. A uniform framework that distinguishes between gene-edited crops and traditional GMOs could facilitate wider acceptance and maintain safety oversight. However, achieving global consensus is difficult due to economic and political factors, including concerns about market control by large biotechnology companies [70]. Scientists and policymakers must work together to develop evidence-based regulations that balance innovation with consumer safety.

Another important factor to be noted is the ethical consideration in the application of CRISPR technology. CRISPR technology holds potential for addressing global food insecurity, yet equitable access remains a concern. Resource-limited regions may struggle to afford CRISPR-enabled agricultural solutions which might exacerbate existing inequalities [71]. Moreover, intellectual property rights concentrated in the hands of a few organizations could restrict the technology's distribution and use in developing countries. Also, the release of CRISPR-edited crops into ecosystems raises questions about long-term environmental impacts. For example, crops engineered for pest resistance may disrupt local biodiversity or lead to the emergence of super-pests through evolutionary pressure [72,73]. Such outcomes show the need for rigorous environmental impact assessments prior to commercialization. Policies promoting open-access CRISPR research and fair licensing practices could prevent monopolization and ensure broader benefits.

The ethical debate surrounding genome editing often centers on “playing God” with nature. While CRISPR lacks the transgenic components of traditional GMOs, it still involves altering natural genomes [15]. Public perception of such interventions varies, with skepticism often fueled by misinformation or a lack of transparency from researchers and companies. Moreover, there is also the issue of informed consent in the sense that the offspring and future generations resulting from the genome editing is not able to give consent at the time of the research and cannot be liable for any mishaps [74]. Hence, there must be regulations in place to draw a clear line between the ethically and generally acceptable use of CRISPR and unacceptable use.

6. Conclusion

CRISPR/Cas9 has been proven to be an important tool in genetic engineering and in addressing global challenges in food security and nutrition. By enabling precise and efficient inheritable genome modifications, this technology heralds a revolutionary age agricultural biotechnology through applications in biofortification, stress resistance, and yield enhancement. It has also been shown to contribute to the development of the nutraceutical industry through various means such as the improvement of secondary metabolite production, the reduction of anti-nutritional factors, and the enhancement of the bioavailability of essential nutrients. Furthermore, the simplicity and adaptability of CRISPR/Cas9 have facilitated its widespread application across diverse plant species and microbial systems, fostering innovation in functional foods and sustainable agriculture.

However, the rapid adoption of CRISPR technology is not without challenges and concerns, most of which stem from ethical and regulatory disparities across countries. These ethical concerns have to be considered and addressed and required regulatory frameworks be installed and adopted in order to unlock the full potential of CRISPR. Also, further research should focus on developing novel materials that are better suited for successful delivery of CRISPR components.

The integration of CRISPR with complementary technologies like nanotechnology and artificial intelligence promises to enhance the efficacy and accessibility of the field. With continued research, collaboration, and general acceptance, CRISPR/Cas9 stands poised to create sustainable solutions for global food security and human health.

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Conflict of Interest

No conflicts of interest related to this work.

Ethical Approval

This research was conducted in compliance with all applicable ethical standards. The study did not involve any human subjects, animals, or hazardous materials.

Data Availability

Data are available on request.

Author Contribution

RAO conceptualize the work. RAO and JTO collated the resources and other materials for the work. The three authors contributed to the writing of the manuscript. ATO edited the manuscript while RAO further carried out visualization and referencing formatting of the work.

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