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REVIEW ARTICLE

Precision genome editing in agriculture: Tacking pathogens through CRISPR-Cas9

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Abstract

Precision genome-editing techniques, in particular CRISPR-Cas9, have revolutionised the management of agricultural diseases by allowing targeted modifications of resistance (R) genes, susceptibility (S) genes and targets of pathogen agents. This transformative approach provides unprecedented control of the interaction between plants and pathogens, enabling the development of crops with increased resistance to a variety of biotic stresses, including bacterial, viral and fungal pathogens. Recent advances have demonstrated the ability of CRISPR-Cas9 to precisely modify key genetic components, while integrating with multi-omics (transcriptomics, proteomics and metabolomics) technologies to identify new mechanisms of resistance and optimise the editing strategy. This development makes it easier to produce new, more stable crops under the pressure of climate change and to tackle critical food security challenges. However, the wide deployment of CRISPR-edited crops faces several obstacles, including regulatory uncertainty, potential unintended effects and public acceptance issues, which need careful consideration. Despite these challenges, CRISPR-Cas9 is a powerful tool for sustainable agriculture, offering precise manipulation of plant immunity and stress response, which contributes to building a more resilient and sustainable global food system. Continued innovation in genome editing, combined with responsible management and public involvement, will be crucial for realizing its full potential in meeting the complex challenges of modern farming.

Keywords: agriculture; biotic stress; CRISPR-Cas9; genome editing; pathogen; R gene

Introduction

Crop improvement, which involves the continuous enhancement of crop genetics to better suit human needs, has been a cornerstone of agricultural development and human civilization (1 - 3). In order to sustainably supply the world's food demands, crop production must increase by 70 % by 2050, when the population is predicted to reach 9.7 billion people (4). However, by intensifying a number of abiotic and biotic pressures, shifting climatic conditions pose serious threats to food security. Among biotic stresses, evolving threats from viruses, fungi, bacteria, nematodes, insects and parasitic plants lead to substantial crop losses, ranging from 30.2 % in rice to 17.2 % in potatoes (5 -7). To address these challenges, researchers are increasingly focusing on genetic modifications to enhance plant resistance to diseases (8, 9). Over millennia, crop improvement has relied on natural variation and selection, a process significantly advanced in 1716 when Fairchild introduced artificial hybridization (10, 11). This was later complemented by mutation breeding and precision techniques (12). Modern plant breeding leverages genome editing, transgenic breeding, mutation breeding and cross-breeding to generate genetic diversity (13, 14). These approaches are particularly vital for increasing crop productivity under shifting climatic conditions (5). Despite advancements like marker-assisted selection, breeding programs still require 6-15 years to develop improved cultivars (15, 16). Mutation breeding, which employs ionizing radiation and chemical mutagens, introduces novel traits but remains unpredictable and labor-intensive. Likewise, the

genetic diversity of the parental genomes limits cross-breeding, which depends on spontaneous mutations. Although transgenic breeding offers the potential for higher yields and improved nutrition, it faces significant regulatory hurdles (17). In contrast, genome editing has revolutionized plant breeding by enabling precise modifications to specific genome regions. Tools like base editors and prime editors allow for high precision and reduced cellular toxicity, significantly improving reliability and efficiency (18, 19). The discovery of Ti plasmids in 1978 and CRISPR sequences in 1987 marked a turning point in plant breeding, enabling precise genome editing to tailor crops with desirable traits (20, 21). These biotechnological advancements have opened new pathways for understanding plant-pathogen interactions and engineering crops to improve disease resistance. Genome editing, in particular, has emerged as a game changing technology, offering unprecedented control over genetic modifications. This review paper provides an overview of plant genome modifications aimed at enhancing disease resistance and explores potential future applications of these technologies. It also examines the benefits and limitations of genome - edited crops, offering insights into their development and utilization for future agricultural innovations.

Methodology

A systematic literature review including peer-reviewed articles, research publications, statistical data from the PubMed, Web of Science and Scopus databases focusing on research publications and review articles on different aspects of agricultural sciences like; disease resistance in various crops and advancements in genome editing techniques was performed. Data were synthesized to summarize recent progress, applications and challenges related to CRISPR-Cas9 technology for crop improvement with emphasis placed on studies reporting experimental validation of pathogen resistance in major crops.

Conventional Vs transgenics Vs genome editing

The procedure of conventional breeding takes a lot of time and effort requiring the cultivation and evaluation of large populations across multiple generations. Despite these challenges, it remains integral to enhancing crop yields. In contrast, genetic engineering offers several advantages over traditional breeding methods. It enables precise insertion, deletion, or modification of specific genes with minimal impact on the rest of the genome, achieving desired traits in significantly fewer generations (22). This technique directly manipulates an organism's genetic material using advanced biotechnological tools, expanding the gene pool by incorporating genetic resources from other organisms. However, genetic engineering is not without its challenges. The random insertion of recombinant sequences from other species, such as viruses or bacteria, raises concerns about unintended effects and the potential disruption of essential genes (23). Additionally, developing genetically modified (GM) crops is both expensive and time-consuming. Regulatory complexities and safety concerns have further hindered their widespread acceptance, with public opinion often skeptical of GM technology (5). Regulatory approaches vary globally, with some countries, such as Switzerland, imposing outright bans on GMOs (24). Genome editing provides a more precise alternative to genetic modification, enabling targeted changes to a plant's DNA, such as specific insertions, deletions, or replacements (25). This precision reduces the risk of unintended genetic disruptions and may offer a pathway to greater public acceptance. Unlike GM crops, genome-edited crops are often subject to less stringent regulatory scrutiny, as seen in countries like Brazil, Argentina and the United States. This regulatory leniency can make genome edited crops more economical and socially acceptable than transgenic crops (10, 26). Despite these advantages, several obstacles persist in the development of disease-resistant crops through genetic engineering. These include limited financial incentives, intellectual property concerns, regulatory hurdles and public skepticism. For example, genetically modified corn (GM MON810) is cultivated only in Spain and Portugal, while most European nations have banned transgenic varieties. In contrast, genome-edited crops have emerged as a promising alternative for addressing biotic stresses. By combining precision, efficiency and cost-effectiveness, genome editing has the potential to overcome many of the challenges associated with traditional genetic modification, paving the way for more sustainable and socially accepted agricultural advancements.

Plant genome editing by site specific nucleases (SSNs)

Genome editing, sometimes referred to as genome engineering, is a state of the art technique that allows for exact modifications at the DNA nucleotide level in living cells. It has revolutionized biological research and industrial applications (27). Plant genomes can be specifically modified using sequence-specific nucleases (SSNs), which target particular DNA sites for cleavage via endonucleases embedded in SSNs. These targets are identified using RNA sequences or DNA-binding domains (15, 28, 29). Following cleavage, the cell's DNA repair mechanisms homologous recombination (HR) or non-homologous end-joining (NHEJ) modify the gene at the targeted site (5,30). The main types of site-specific nucleases (SSNs) include meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and the CRISPR system (5, 18, 31). These technologies have significantly enhanced the precision, efficiency and cost-effectiveness of genome editing (18, 31).

Meganucleases, described as naturally occurring endonucleases in 1985, were the first tools capable of producing double-strand breaks (DSBs) in genome editing (32). They can recognize long DNA sequences of 14-40 base pairs, exemplified by I-SceI, the first meganuclease identified in yeast (5, 27). Meganucleases induce homologous recombination in plant cells with high specificity, making them effective for targeted genetic engineering. The first instance of precise genetic engineering using meganucleases in plants occurred in 1993, when I-SceI-induced DSBs facilitated homologous recombination in *Nicotiana tabacum* (5). Despite their specificity and low toxicity compared to other techniques like ZFNs, meganucleases face significant challenges. Their utility is limited by sequence degeneracy, low catalytic activity and an underdeveloped DNA-binding structure (33, 34). The extensive protein engineering required for each new target sequence increases costs and time commitments. Additionally, patent issues complicate their use for expanding target sequences (2). ZFNs are chimeric proteins that function as molecular scissors by combining two essential components: a DNA-binding domain and a cleavage domain derived from the FokI enzyme. The DNA-binding domain uses zinc finger modules to recognize specific genome sequences with high precision (35). Each zinc finger can recognize three base pairs and by linking 6 or 8 zinc fingers, ZFNs can bind to sequences approximately 20 base pairs long. The FokI

domain dimerizes to induce DSBs in the DNA, enabling site-directed mutations (36, 37). ZFNs were first recognized as SSNs in 1996, offering high efficiency in somatic cells. However, their application in germ cells has been less successful due to inefficiencies, low repeatability and the complexity of designing unique protein domains for each genomic locus (38, 39). Off-target effects, potential cytotoxicity from unintended cleavage and single nucleotide alterations further limit their precision (40). Despite their potential, ZFNs face challenges in practical application. Designing and customizing ZFN constructs involves costly and labor-intensive biophysical computations (2). These limitations, coupled with the risk of domain interactions and the possibility of off-target effects, have restricted their widespread use in crop editing (41).

Zinc finger nucleases (ZFNs) have been widely used for genome editing but face limitations due to high costs, complexity and safety concerns. This has prompted a shift toward alternative technologies, such as TALENs and CRISPR/Cas systems. TALENs, inspired by transcription activator-like effectors (TALEs) produced by phytopathogenic bacteria like *Xanthomonas*, were first introduced in 2011 (42, 43). These nucleases combine a FokI endonuclease domain with customizable TALE DNA-binding domains, functioning as artificial restriction enzymes for precise genome editing (5, 44). TALENs can target virtually any nucleotide sequence, guided by their DNA-binding domains, which consist of 34-amino-acid repeats. Sequence specificity is determined by repeat variable di-residues (RVDs) at positions 12 and 13, with binding efficacy influenced by the presence of thymidine at the target sequence's 5' end (45).TALENs were first used in crop improvement by editing the *OsSWEET14* gene in rice, conferring resistance to bacterial blight (46). These nucleases induce double-strand breaks (DSBs) at target sites, separated by a short spacer sequence, using their FokI catalytic domains (27). However, their adoption is hindered by challenges such as the large size (~3 kb) of TALEN cDNA, making cellular delivery difficult and the complexity of designing TALE repeats (47).

In contrast, the CRISPR/Cas system has revolutionized genome editing due to its simplicity, efficiency and cost-effectiveness. First identified in *E. coli*) as unique 29 nucleotide repeats interspersed with spacers (48), its functional significance was clarified in subsequent studies (49). Jansen et al. coined the term "CRISPR" in 2002 (50). In 2013, the CRISPR/Cas9 system emerged as a breakthrough tool for genome editing, enabling precise alterations by introducing DSBs into DNA (51). These breaks are repaired via homology-directed repair (HDR) or non-homologous end joining (NHEJ), guided by Cas9 protein and a single guide RNA (sgRNA) (19, 52). Cas9, derived from *Streptococcus pyogenes*, is the most commonly used nuclease for plant genome editing due to its high precision and efficiency (53). Variants like Cas12a (Cpf1) offer unique advantages, such as smaller size, PAM flexibility and simultaneous editing of multiple genes (54, 55). Cas13 targets single-stranded RNA (ssRNA) for RNA interference applications, while Cas14 provides enhanced specificity without requiring a protospacer adjacent motif (PAM) (5, 56).CRISPR-based DNA-free approaches minimize off-target effects by avoiding foreign DNA integration (15). While NHEJ-mediated DSB repair is commonly used for gene knockouts, HDR offers greater precision, albeit with lower efficiency in plants (13, 57). DNA insertion using donor templates via NHEJ has been demonstrated, as in CRISPR/Cas9-mediated intron targeting for gene replacement (58, 59).

A comparative anslysis between different genome editing tools have been provided in Table 1. The success in site-specific mutagenesis across various plant species, CRISPR/Cas9 continues to evolve, with ongoing advancements aimed at addressing technical challenges and broadening its applications (5). These developments underscore the growing potential of CRISPR/Cas systems as transformative tools in genome editing, surpassing traditional methods like ZFNs and TALENs in precision, scalability and accessibility.

Disease management through CRISPR-Cas

Plant breeding and research have consistently aimed to enhance crop tolerance to diseases, employing cutting-edge techniques to modify genetic architecture. These range from point mutations to the insertion of chromosomal segments from wild relatives into cultivated species, addressing various biotic stresses (7). Traditional approaches, including extensive crosses, natural mutations, hybridization and random mutagenesis, have generated numerous disease-resistant plant varieties. Mutagenesis methods, such as chemical agents like ethyl methanesulfonate (EMS), physical agents like X or γ radiation and biological mutagenesis via transposons, have been extensively used. However, these methods have limitations, such as randomness, labor intensity and time consumption, making forward mutation approaches less efficient for identifying and producing specific gene knockout lines (7). Targeting resistance (R) genes through genome editing offers a promising strategy to enhance plant immunity by engineering pathogen recognition. Precision editing of R genes (e.g., NLRs) using CRISPR-Cas9 can enable stacking of multiple alleles, however, their rapid co-evolution with pathogen effectors and functional redundancy within gene clusters pose challenges for durability. As an alternative to R-gene-mediated approaches, susceptibility (S) genes have emerged as promising targets for

Table 1. A comparison between different genome editing tools: CRISPR vs. ZFNs vs. TALENs

Feature	CRISPR-Cas9	Zinc finger nucleases (ZFNs)	TALENs
Mechanism	RNA-guided (gRNA + Cas9 nuclease)	Protein-guided (Zinc finger + FokI)	Protein-guided (TALE + FokI)
Precision	High (with optimized gRNA)	Moderate (off-target effects common)	High (specific TALE binding)
Efficiency	Very high (easy multiplexing)	Low to moderate (depends on ZF design)	Moderate (efficient but laborious)
Design complexity	Simple (gRNA design via software)	Complex (protein engineering required)	Complex (TALE repeat assembly needed)
Cost	Low (cheap RNA synthesis)	High (patent/licensing costs)	High (time-intensive protein design)
Off-target effects	Moderate (improved with HiFi Cas9)	High (due to zinc finger promiscuity)	Low (highly specific binding)
Multiplexing	Excellent (multiple gRNAs at once)	Poor (difficult to engineer)	Limited (possible but cumbersome)
Delivery	Easy (plasmid, ribonucleoprotein)	Challenging (large protein size)	Challenging (large cDNA size)
Applications	Broad (plants, animals, microbes)	Limited (mostly mammalian cells)	Broad (but less adopted than CRISPR)
Future improvements	Base/prime editing, reduced off-targets	Improved specificity, reduced toxicity	Simplified TALE assembly, cost reduction

Table 2. A comparative analysis of targeting strategies for genome editing of R and S genes in plants

Aspect	Editing R genes	Editing S genes
Approach	Enhance expression or stack multiple R genes (e.g., *Xa21* in rice)	Knockout or disrupt function (e.g., *MLO* for powdery mildew resistance)
Precision needed	High (must preserve signaling domains)	Low (complete loss of function often sufficient)
Durability	Pathogen may evolve to evade recognition	Broad-spectrum resistance (pathogen cannot adapt easily)
Off-Target Risks	Higher (R genes often exist in clusters with functional redundancy)	Lower (single gene disruption)
Advantages	-Natural defense mechanism -Can be stacked for multiple pathogens -May avoid pleiotropic effects (unlike S gene knockouts)	-Broad-spectrum resistance. -Fewer off-target effects. -Durable (pathogens cannot easily bypass loss of host factor)
Limitations	-Pathogen adaptation (e.g., effector mutations) -Complex regulation (editing may disrupt immune balance)	-Pleiotropy (e.g., *SWEET* knockouts may affect plant development). - Limited to known S genes

durable disease resistance. *S* genes encode proteins that pathogens exploit to suppress plant immunity or facilitate their own development, often acting as negative regulators of immunity (Table 2). Disrupting or inactivating these genes can effectively prevent disease progression without affecting host viability. For instance, the *Pi21* gene in rice confers recessive resistance to *Magnaporthe oryzae*, the pathogen responsible for blast disease. Natural alleles of *Pi21* contain small deletions in a proline-rich region at the C-terminus (60). Another notable example is *mlo*-based resistance in barley, first identified in an Ethiopian barley landrace during the 1940s. The *MLO* gene, associated with mildew resistance, has been a cornerstone of European crop breeding programs for over 40 years (61, 62). Homozygous plants carrying the recessive *mlo* allele in barley, tomato and *Arabidopsis* exhibit broad-spectrum resistance to powdery mildew (7, 63, 64). In contrast, traditional breeding approaches have primarily focused on *R*-gene-based resistance, which involves transferring nucleotide-binding leucine-rich repeat receptors (NLRs) across species to achieve broad-spectrum resistance (65). While effective, the reliance on *R*-gene-based resistance in monoculture systems poses significant challenges. Monocultures exert substantial selection pressure on pathogens, driving effector diversity and pathogen adaptation. Additionally, nucleotide-binding leucine-rich repeat receptors (NLRs) often have a narrow range of pathogen recognition (59,66 - 68). Despite these limitations, genetic modifications incorporating single or stacked *R* genes have achieved durable resistance against diseases and pests (68 - 70). The advent of modern genome-editing technologies such as zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and CRISPR-Cas systems has revolutionized plant research and resistance breeding by enabling precise genetic modifications (71-73). These tools employ nucleases like Cas9 and TALENs to introduce sequence-specific double-strand breaks (DSBs), which are repaired through the plant's natural mechanisms, primarily non-homologous end joining (NHEJ) or, less frequently, homology-directed repair (HDR) (74, 75). While HDR facilitates precise gene replacement using a donor template, NHEJ often introduces small insertions or deletions (indels) at the target site. A notable application of CRISPR technology includes the deletion of the *BSR-K1* gene in rice, conferring resistance to *Magnaporthe oryzae* and *Xanthomonas oryzae pv. oryzae* (Xoo) and the repair of defective R genes through precision base editing to enhance disease resistance (76). These advancements are transforming crop improvement by creating resilient varieties, reducing reliance on traditional breeding and addressing challenges from evolving pathogens (Fig. 1).

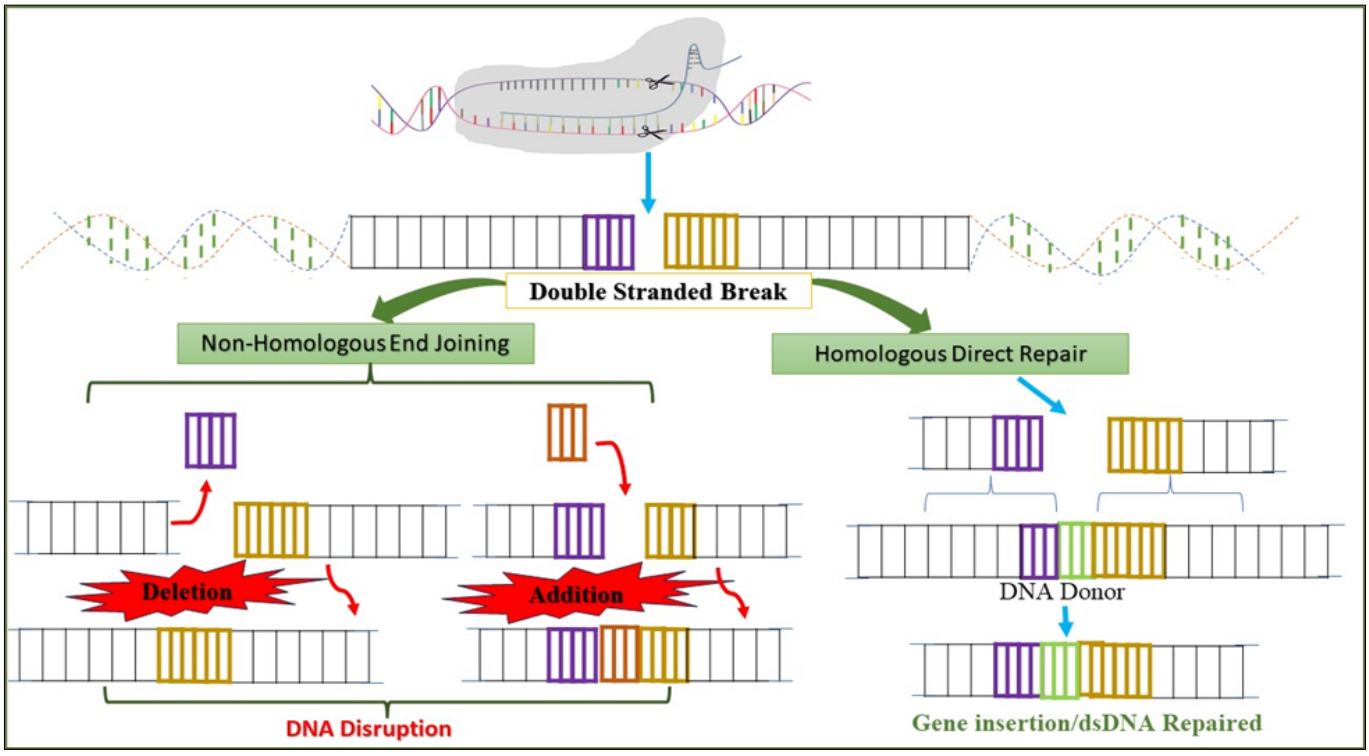

Fig. 1. This figure demonstrates various applications of CRISPR-Cas technology in genome editing through Non-homologous end joining (NHEJ) and Homologous direct repair (HDR).

Virus

The CRISPR-Cas system, derived from bacterial immune mechanisms, has emerged as a powerful tool for engineering virus-resistant plants by precisely targeting and cleaving DNA or RNA sequences. Platforms utilizing Cas9 or Cas13a have demonstrated significant success against both DNA and RNA viruses (Table 3). For example, resistance to Tomato Yellow Leaf Curl Virus (TYLCV) has been achieved in *Nicotiana benthamiana* and tomato using SpCas9 and guide RNAs targeting viral genome regions, while similar approaches have conferred resistance to other geminiviruses like Beet Severe Curly Top Virus (77, 78). In rice, editing the *eIF4G* gene with CRISPR/Cas9 produced plants resistant to Rice Tungro Virus, improving yields and eliminating viral protein expression (5). RNA-targeting CRISPR systems, such as Cas13a, have also been employed to combat RNA viruses like Turnip Mosaic Virus without inducing off -target mutations, while FnCas9 has been effective against Cucumber Mosaic Virus and Tobacco Mosaic Virus (47, 79). Furthermore, the eukaryotic translation initiation factor *eIF4E*, essential for many viral infections, has been targeted to enhance

Table 3. Comprehensive overview of genome editing applications for enhancing disease resistance in different agricultural crops

Technique	Crops	Targeted genes/Target Area	Improved traits/Results	References
MN	Cotton	*cry2Aelbar* transgene locus site	Insect resistance stacking	(118)
ZFN	Tobacco	Rep	DNA viral disease (TYLCCNV and TbCSV)	(119)
TALEN	Wheat	*TaMLO-A1, TaMLO-B1, TaMLO-D1*	Powdery mildew Resistance	(21)
	Rice	*OsSWEET14*/promoter	Enhanced disease resistance (*Xanthomonas oryzae* pv. *Oryzae*)	(120)
	Tobacco	Rep	Disease resistance (TbCSV, TYCCNV and TLCYnV) (Partial)	(120)
	Triticum aestivum	*TaABCC6, TaNFXL1, TansLTP9.4*	Defense against fusarium head blight disease	(21)
		TaMLO homologs	Repress resistance pathway to powdery mildew	(59)
		TaMLO-A1, TaMLO-B1 and TaMLOD1	Powdery mildew disease (*Blumeriagraminis f. sp. tritici*)	(59)
		TaEDR1	Enhanced disease resistance (Powdery mildew)	(121)
		TaNFXL1	*Fusarium graminearum* resistance	(122)
		TaLpx-1	Enhanced resistance to disease (*Fusarium graminearum*)	(123)
	Barley	*MP, CP, Rep/Rep, IR*	No disease symptoms and virus presence, (Wheat Dwarf Virus (WDV))	(121)
	Oryza sativa	*OsSWEET11, OsSWEET14, OsSWEET13* (Rice bacterial blight susceptibility genes	Bacterial blight of rice	(124)
		OsERF922 (Ethylene responsive factor transcription factor)	Rice blast disease Resistance	(124)
		Os8N3/promoter	Bacterial Blight Resistance	(121)
		OsERF922	Rice blast Resistance	(121)
		eIF4G	Rice tungro disease Resistance	(121)
		Pi21/cds region	Enhanced disease resistance (Rice blast)	(120) et al., 2020
		OsCul3a	*Xanthomonas oryzae*/*Magnaporthe oryzae* resistance	(125)
	Gossypium hirsutum	CLCuD IR and Rep regions	Cotton leaf curl disease	(124)
		Gh14-3-3d	Enhanced resistance to disease (*Verticillium dahlia*)	(123)
	A. thaliana/ N. benthamiana	dsDNA of virus (A7, B7 and C3 regions)	Beet severe curly top virus resistance	(126)
	Arabidopsis thaliana	elF(iso)4E (elF transcription factor	Turnip mosaic virus disease	(81)
CRISPR/Cas9	*N. benthamiana*	ORFs and the IR sequence sDNA of virus	Tomato yellow leaf curl virus (TYLCV) and Merremia mosaic virus (MeMV)	(77)
		BeYDV	Bean yellow dwarf virus (BeYDV) resistance	(126)
	Glycine max	GmUGT	Enhanced resistance to *Helicoverpa armigera* and *Spodoptera litura*	(5)
		GmF3H1/2, FNSII-1	Soybean mosaic virus	(122)
	Cucumis sativus L.	elF4E (eukaryotic translation initiation factor 4E)	Ring spot disease, vein yellowing disease (virus-resistant heterozygous non-transgenic mutants created through eLF4E disruption), resistance to CVYV, ZYMV and PRSMV.	(124)
	Tomato	SlDMR6-1/Host S-gene	Bacterial disease Resistant plants	(5)
		SlMlo1	Resistance to powdery mildew (*O. neolycopersici*, Powdery mildew)	(127)
		Tomato	Resistance against *Pseudomonas syringae*, *Phytophthora capsici* and *Xanthomonas spp.*	(127)
		SlJAZ2	Enhanced disease resistance and defence trade-off solved (*P. syringae* pv. tomato (Pto)) DC3000	(128)
		SlPMR4	Enhanced disease resistance, (*O. neolycopersici*, Powdery mildew)	(129)
		Solyc08g075770/genomic region	Enhanced susceptibility to disease (Fusarium wilt)	(120)
		SlMAPK3	Enhanced susceptibility to disease (Gray mold)	(120)
	Grape	MLO-7	Powdery mildew (Indels in target, resistance not confirmed)	(127)
	Apple	DIPM-1, DIPM-2 and DIPM-4	Enhanced disease resistance (Fire blight)	(121)
	Banana	eBSV	Banana Streak Virus (BSV)	(130)
		RGA2, Ced9	Significant reduction in disease (Fusarium wilt caused by *Fusarium oxysporum f. sp. cubense* tropical race 4 (TR4))	(131)
	Cacao	TcNPR3	*Phytophthora tropicalis* (Enhanced disease resistance)	(132)
	Papaya	alEPIC8	Enhanced disease resistance (Root, stem and fruit rot)	(133)
	Cassava	nCBP-1 and nCBP-2/cds region	Reduced virus load and symptoms (CBSV)	(120)
	Capsicum annuum	CaERF28	*Anthracnose* disease resistance	(134)
	Citrus	CsLOB1	Citrus canker resistance	(99)

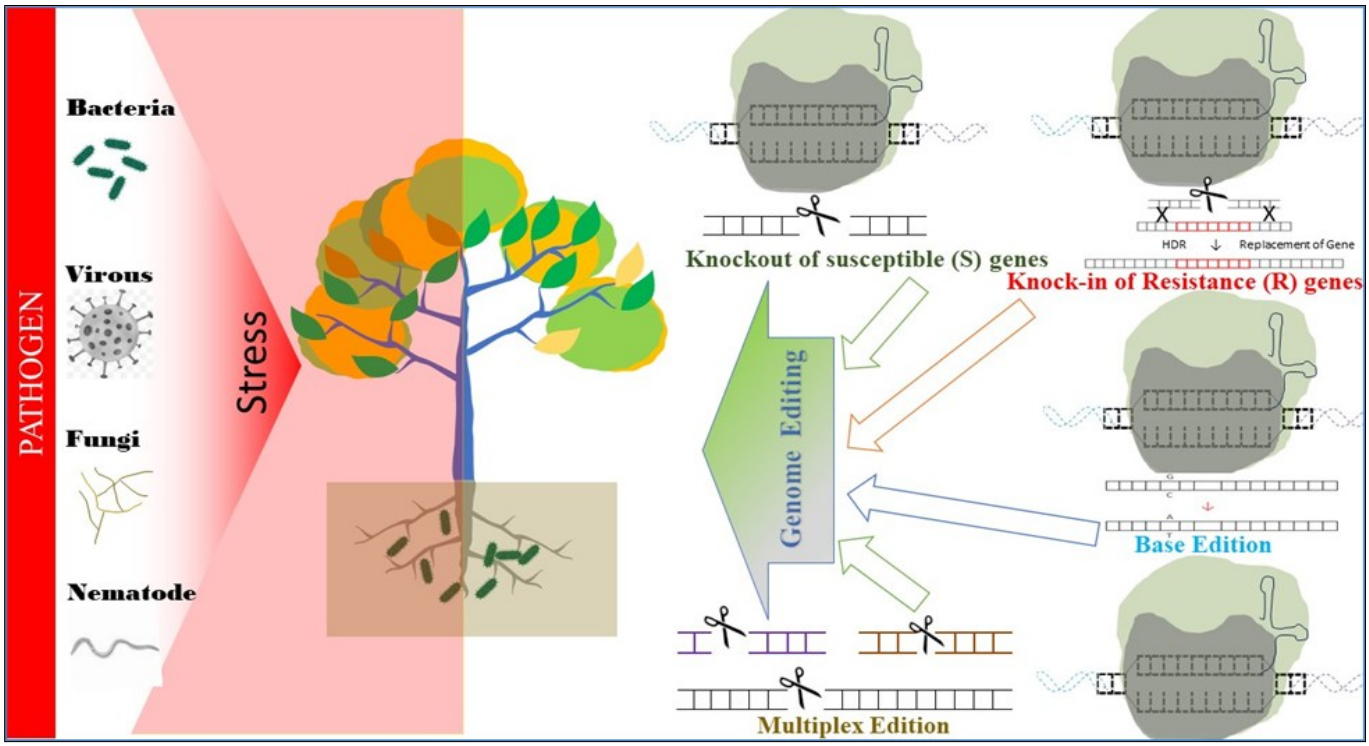

Fig. 2. This figure illustrates the use of CRISPR-Cas technology in advancing disease resistance plant development by knocking out the susceptible genes.

resistance. For instance, knocking out *eIF4E* in cucumbers and Arabidopsis rendered plants resistant to multiple viruses, including Cucumber Vein Yellowing Virus and Turnip Mosaic Virus, without compromising growth (80, 81). These advancements illustrate the transformative role of genome-editing technologies in creating virus-resistant crops, with promising implications for sustainable agriculture (Fig. 2).

Bacteria

Plant disease management often involves genetic resistance, agronomic practices and biocontrol agents (82). Rice bacterial blight, caused by *Xanthomonas oryzae*pv. *oryzae* (Xoo), is a major threat to crop yields, with losses typically ranging from 10-20 % and escalating to over 50 % or complete crop failure under high humidity conditions (83). A promising strategy to combat this disease leverages CRISPR/Cas9 genome editing to target the *OsSWEET14* gene, also known as *Os11N3*. This gene encodes a sugar transporter protein from the MtN3/saliva/SWEET family, originally identified in *Medicago truncatula* roots inoculated with *Rhizobium meliloti* through expression screening. Pathogens frequently exploit sucrose transporters encoded by SWEET genes to facilitate infection. By editing the promoter regions of *OsSWEET* genes using CRISPR/Cas9, researchers have achieved significant resistance to bacterial leaf blight, demonstrating the potential of this technology in disease management for rice (84, 85).Knocking out the *OsERF922* gene using CRISPR/Cas9 has significantly improved tolerance to leaf blast disease (86). SWEET genes, which encode transmembrane sugar transporters, play a pivotal role in the pathogenicity of numerous plant diseases (87, 88). In rice, *Xanthomonas oryzae*pv. *oryzae* (Xoo) TAL effectors target *OsSWEET11* and *OsSWEET14* promoters, enhancing sugar efflux into the apoplast and facilitating bacterial colonization (89-92). For example, the TAL effector protein AvrXa7 from the Philippine strain PXO86 binds to effector-binding elements (EBEs) in the *OsSWEET14* promoter, inducing its expression and enabling the pathogen to exploit *OsSWEET14* as a sucrose efflux transporter, thereby promoting virulence (93). Other Xoo TAL effectors, such as PthXo1, PthXo2, PthXo3, TalC and Tal5, bind distinct EBEs in SWEET gene promoters, further driving sugar efflux and bacterial proliferation (7, 94). Recognizing SWEET genes as susceptibility factors, researchers have focused on engineering resistance through precise genome modifications (7). Since SWEET genes are essential for plant development, complete knockout strategies are not viable (94, 95). To address this, previous works utilized designer TAL effectors (dTALEs) combined with FokI nucleases to edit EBEs in the *OsSWEET14* promoter (46). This approach introduced small indels in overlapping EBEs, effectively preventing pathogen-induced gene expression without disrupting normal plant development, thereby conferring resistance to multiple Xoo strains (46). Similarly, CRISPR/Cas9-mediated mutations in the *SWEET11* promoter have demonstrated resistance to Xoo (96), while additional studies confirmed that CRISPR-Cas modifications in the *SWEET14* promoter enhance resistance in rice protoplasts (97).

Given the essential role of *OsSWEET14* in development, TALENs were engineered to specifically target effector-binding elements (EBEs) in its promoter. This strategy blocked AvrXa7 binding without compromising the gene's developmental functions (46). Similarly, targeted modifications to EBEs for AvrXa7 and Tal5, providing resistance to *Xanthomonas oryzae* pv. *oryzae* (Xoo) strains dependent on these TAL effectors (7, 98). These advancements highlight the potential of precision genome editing in engineering broad-spectrum disease resistance and enhancing crop resilience (85). Beyond bacterial blight, CRISPR/Cas9 has enabled resistance to other plant diseases. For instance, editing the *bsr-k1* gene in rice conferred resistance to both bacterial leaf blight and leaf blast by disrupting a gene responsible for the turnover of defense-related genes (5, 76). Similarly, efforts to manage citrus canker, caused

by *Xanthomonas citri* ssp. *citri* (Xcc), have focused on editing the *CsLOB1* gene. This gene regulates plant growth and susceptibility and deleting an EBE in its promoter significantly reduced Xcc-induced canker formation, thereby enhancing resistance (99). Targeting both the coding region and promoter EBEs of *CsLOB1* further strengthened resistance (99, 100). In *Arabidopsis thaliana*, EMS mutant screenings identified the *DOWNY MILDEW RESISTANT6* (*DMR6*) gene as a critical regulator of plant immunity. Mutants such as *dmr3*, *dmr4*, *dmr5* and *dmr6* were shown to activate pathogenesis-related (*PR*) gene expression even in the absence of pathogens, underscoring their role in suppressing immunity (7, 101, 102). These findings underscore the transformative potential of genome editing in developing durable and broad-spectrum disease resistance, offering a promising path toward more resilient crops.

Tomatoes, an essential crop with significant economic importance, are highly vulnerable to several devastating diseases caused by pathogens such as *Pseudomonas syringae* and *Xanthomonas* species (103). Infections by *P. syringae* pv. *tomato* and *Phytophthora capsici* have been shown to upregulate the expression of the tomato orthologue *SlDMR6-1*. Targeted mutations in *SlDMR6-1* using CRISPR/Cas9 have proven effective in maintaining elevated salicylic acid levels, which significantly reduce pathogen proliferation and disease symptoms. This genome-editing approach provides resistance to *P. syringae*, *P. capsici* and various *Xanthomonas* species, while preserving normal tomato growth and development (5).This approach builds on insights from the *Arabidopsis* susceptibility gene *DOWNY MILDEW RESISTANT6 (DMR6)*, which encodes an oxygenase that is upregulated during pathogen infection (101, 102, 104). In tomatoes, two orthologues of *DMR6-SlDMR6-1* and *SlDMR6-2* were identified through translational research. Of these, only *SlDMR6-1* exhibited increased expression following infection by *Pseudomonas syringae* pv. *tomato* or *Phytophthora capsica* (105, 106). To disrupt *SlDMR6-1* function, CRISPR/Cas9 was employed to introduce small insertions and deletions (indels) in exons 2 and 3, specifically targeting the enzyme's active site. This genetic modification produced mutant tomato plants expressing truncated forms of the *SlDMR6* protein. Tests on a homozygous T1 mutant line with a 7-bp deletion in exon 3 revealed broad-spectrum partial resistance against various pathogens, including *Xanthomonas gardneri* Xg153, *Xanthomonas perforans* Xp4b, *P. syringae* DC3000 and the oomycete *P. capsici* LT1534. Crucially, this resistance was achieved without compromising plant growth or morphology (7). Phylogenetic and gene expression studies further confirmed that *SlDMR6-1* is the sole functional *DMR6* orthologue in tomatoes, reinforcing its role in susceptibility. Greenhouse experiments also demonstrated heightened resistance to *P. syringae* in *SlDMR6-1* knockout plants edited with CRISPR/Cas9. By targeting susceptibility genes (*S* genes) and negative regulators of innate immunity, CRISPR/Cas9 has emerged as a highly effective strategy for bolstering plant defenses (Table 3). This precision genome-editing tool holds immense promise for developing crops with enhanced resilience to a wide array of pathogens.

Fungi

Fungi are a leading cause of plant diseases, posing significant challenges to agriculture due to their diverse lifestyles, genetic adaptability and ability to overcome both R gene-mediated resistance and fungicides (107). Among these diseases, powdery mildew is particularly widespread and destructive. In barley, CRISPR/Cas9-mediated editing of the *MORC1* gene has demonstrated enhanced resistance to *Fusarium graminearum* and barley powdery mildew, resulting in reduced lesion formation and fungal DNA levels (5). A pivotal advancement in breeding for durable and broad-spectrum resistance to powdery mildew was the discovery of *mlo* (mildew resistance locus o) mutants in barley (108). The *MLO* gene, first identified in barley, is a classical susceptibility (*S*) gene that makes plants vulnerable to all known isolates of *Blumeria graminis* f. sp. *hordei* (Bgh) (61). *MLO* encodes a plasma membrane-associated protein that interacts with calmodulin through its C-terminal cytoplasmic tail and exhibits structural similarity to G-protein-coupled receptors in metazoans. Its role in susceptibility has been validated across multiple plant species (7, 62-64, 109, 110). Genome editing, particularly with CRISPR/Cas9, has enabled targeted modifications of *MLO* homologs in various crops, significantly enhancing resistance to powdery mildew. For instance, CRISPR/Cas9 editing of three *MLO* homologs (*TaMLO-A*, *TaMLO-B* and *TaMLO-D*) in wheat increased resistance to the disease (5). Similarly, genome-editing tools like TALEN and CRISPR/Cas9 have been employed to knockout *MLO* genes in wheat and tomato, effectively conferring resistance to powdery mildew pathogens (59, 111).These advances underscore the transformative potential of genome-editing technologies in combating fungal diseases and enhancing crop resilience. For example, targeting conserved regions of the *MLO* exon 2 in wheat with CRISPR/Cas9 and TALENs has generated *mlo* mutant plants exhibiting significantly enhanced resistance to *Blumeria graminis* f. sp. *hordei* (Bgh). These mutants showed no visible fungal growth compared to wild-type plants (59). Similarly, CRISPR/Cas9 editing of *SlMlo1* in tomatoes resulted in transgene-free plants resistant to *Oidium neolycopersici* (111).

Beyond *MLO* genes, other susceptibility and negative regulatory genes have also been targeted to enhance disease resistance. For instance, simultaneous editing of three wheat *TaEDR1* homologs using CRISPR/Cas9 improved resistance to powdery mildew (112). These developments highlight the significant potential of genome editing to revolutionize plant disease management and promote sustainable agriculture.In rice, resistance to *Magnaporthe oryzae*, the causative agent of rice blast, has been improved by targeting the negative regulatory gene *OsERF922*. Using RNA interference, silencing *OsERF922* enhanced resistance to rice blast. Similarly, CRISPR/Cas9-mediated editing of *OsERF922* in the japonica rice variety Kuiku131 conferred increased resistance without negatively affecting plant growth (7, 86). ERF transcription factors play pivotal roles in plant immunity, acting as both positive and negative regulators. Overexpression of specific ERFs has been shown to enhance stress tolerance and resistance to various pathogens (113 - 115). Conversely, suppressing negative regulatory ERFs, such as potato *ERF3*, has increased resistance to *Phytophthora infestans* (116). In cotton, CRISPR/Cas9-mediated knockout of negative regulators *14-3-3c* and *14-3-3d* effectively reduced pathogen presence and mitigated disease symptoms, thereby enhancing resistance to *Verticillium dahlia* (5, 117). These findings underscore the versatility and efficiency of CRISPR/Cas9 technology in targeting susceptibility genes and negative regulators of plant immunity (Table 3). By leveraging this approach, it is possible to develop crops with broad-spectrum pathogen resistance, significantly contributing to agricultural resilience and sustainability.

Table 4. A comparative analysis on global regulations on genome edited crops

Region	Regulatory approach	Key policy updates (2023-2025)	Approved gene-edited crops
USA	Product-based (non-GMO if no foreign DNA)	USDA streamlined approval process (2024)	• Non-browning mushrooms (2016) • High-oleic soybeans (2021) • Reduced-bitter mustard greens (2023)
European Union(EU)	Process-based (treated as GMOs)	Proposed NGT-1/NGT-2 classification (2025 implementation)	None (treated as GMOs)
India	Case-by-case (SDN-1/2 exempt)	DBT released biosafety guidelines (2024)	• CRISPR mustard DMH-11 (2023) • High yield DRR Dhan 100 (2025) • Salinity tolerant Pusa DST Rice-1(2025)
China	Mixed (research encouraged, strict approvals)	New biosafety law implemented (2023)	• High-yield soybeans (2024)
Japan	Fast-track for non-transgenic	Updated guidelines for consumer labeling (2024)	• GABA-enhanced tomato (2021) • Heart-healthy sardines (2023)

Global regulations of genome edited crops

The regulatory approaches used in the international governance of genome-edited crops are complicated and reflect fundamental variations in risk perception, agricultural priorities and public acceptance among jurisdictions. Product-based, process-based and hybrid systems are the three general categories into which current frameworks can be divided (Table 4). Both the US and Canada use their respective agencies (USDA-APHIS and CFIA) to implement a product-focused regulatory approach in North America. Their 2020-2022 policy revisions stated that, as long as they don't contain any foreign DNA, plants created by genome editing that could potentially be produced through traditional breeding are exempt from GMO regulations. Several innovative crops, such as Pairwise's nutrient-enhanced greens (2023) and Calyxt's high-oleic soybeans (approved in 2019), have been made commercially viable as a result. The FDA does, however, continue to conduct voluntary consultations for food safety assessments, which raises some questions in the market (135). The European Union has the world's strongest process-based regulation since its contentious 2018 ECJ judgment (Case C-528/16), in which all genome-edited organisms were deemed GMOs. But in 2023, there was a big policy change with the European Commission suggesting that some classes of NGTs (New Genomic techniques) be exempted from Directive 2001/18/EC. Asia offers a diverse regulatory environment for genome edited crops. Japan was one of the first to adopt, with its guidelines of 2019 making a distinction between transgenic and non-transgenic variants. This paved the way for the launch of a GABA-enriched tomato from Sanatech in 2021, marketed directly to consumers. China is one of the major investor in genome-editing research, but has a strict policy on commercialisation, even though field trials of CRISPR wheat in 2024 suggest that approval is imminent. The Govt. of India guidelines on genome editing (2022) created a middle ground, exempting SDN-1 and SDN-2 from strict GMO regulation, but subjecting them to case-by-case review as in the approval of mustard edited with CRISPR in 2023 and release of two genome edited rice varieties DRR Rice 100 (Kamla) and Pusa DST Rice 1 for commercial cultivation in 2025 (136).

Many developing countries are now developing more flexible regulations for gene-edited crops. Argentina and Brazil have led the way in Latin America in implementing science friendly policies from 2019 to 2021. In Africa, progress is slower but is moving ahead - Nigeria has set 2022 as the date for introducing its first rules on gene-editing and Kenya is working on a similar plan. These changes show that more countries understand that gene-editing can help to grow crops that can survive drought, pests and other climatic challenges (135).

Future prospect and Conclusion

Although CRISPR-Cas9 has shown remarkable potential for developing disease resistant crops, to fully realise its potential, several critical gaps need to be addressed. Present research is often focused on model crops and well characterised pathogens, which leaves important gaps in the modification of non-model species and complex systems, in particular in forest trees and perennial crops. Moreover, the long term environmental effects of gene edited crops in different agroecosystems are note well documented. Future research may be focused on extending CRISPR to orphan crops and woody species, optimising delivery systems for resistant plants, refining accurate gene insertion and stacking methods for stable trait expression and developing robust frameworks for environmental risk assessment to enable responsible use of engineered crops. Moreover, integrating CRISPR with emerging technologies such as synthetic biology and AI driven gene design could speed up the development of climate-resilient crops. What is crucial is the need for interdisciplinary-disciplinary cooperation between molecular biologists, breeders, ecologists and social scientists to tackle technical challenges while ensuring public acceptance and equitable access to these technologies. By focusing on these actionable priorities, the scientific community can translate the potential of CRISPR into tangible solutions to global food security while preserving the balance of the environment. Investments in these directions will determine whether genome editing will become a transformative tool for sustainable farming or whether it will remain limited to incremental improvements in select crops.

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Authors' contributions

BK, PU, RRK and TR wrote original draft and analysed data. RK, KR, VK, RB, MK, SKJ and AK participated in the conceptualization, supervision, validation, review and editing. All authors read and approved the final manuscript.

Compliance with ethical standards

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