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Review

# Molecular Basis of Plant-Pathogen Interaction in the Agriculture Context

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**Simple summary:** Plants encounter several biotic and abiotic challenges during their life cycle. Biotic stressors pose serious threats to crop yield, causing food security issues. Different signaling pathways such as recognition receptors help to recognize pathogen invasion and activate the plant defense response. Understanding the plant-pathogen-interaction at molecular level is crucial for developing strategies to enhance resistance and mitigate the impact of plant diseases on agriculture productivity.

**Abstract:** Biotic stressors pose serious threats to crop yield, jeopardizing food security and resulting in over US\$220 billion per year losses to the agriculture industry. Plants activate innate defense mechanisms upon pathogen perception and invasion. The plant immune response comprises numerous concerted steps, including the recognition of invading pathogens, signal transduction, and activation of defensive pathways. However, pathogens have evolved various structures to evade plant immunity. Given these facts, genetic improvements of plants are required for sustainable disease management to ensure global food security. Advanced genetic technologies have provided new opportunities to revolutionize and boost plant disease resistance against devastating pathogens. Furthermore, targeting susceptibility (S) genes, such as *OsERF922* and *BnWRKY70*, through CRISPR methodologies offers novel frontiers to disrupt the molecular compatibility of pathogens and introduce durable resistance against them in plants. Here, we provide a critical overview of advances in understanding disease resistance mechanisms. The review also critically examines management strategies under challenging environmental conditions and *R* gene-based plant genome engineering systems intending to enhance plant responses against emerging pathogens. This work underscores the transformative potential of modern genetic engineering practices in revolutionizing plant health and crop disease management while emphasizing the importance of responsible application to ensure sustainable and resilient agricultural systems.

**Keywords:** Agriculture; climate change; pathogens; resistance mechanisms; genome engineering

## 1. Introduction

Agriculture is the most important sector as it provides raw materials for the feed and food industries. The world population is currently increasing by approximately 1.1% per year [1], and if this trend continues, the global population is projected to reach 9.9 billion by 2050 [2]. Consequently, global food production needs to increase by 70% to effectively meet the nutritional requirements of the growing population [3]. While climate-driven constraints threaten crop production worldwide [4]. At least half of the loss in agricultural production systems is due to biotic stresses imposed by pathogenic fungi, bacteria, viruses, and nematodes [5]. In some cases, new races of pests and diseases have resulted in global yield losses ranging from 10% to 40% [6], impacting the agriculture industry with annual losses exceeding US\$220 billion [7]. For instance, emerging strains of wheat blast [8,9] and wheat stem rust fungus Ug99 [10] severely reduced wheat production by 15% in 2017 and 2018.

Usually, chemical fungicides and pesticides have been extensively used to control plant diseases, but their excessive use has resulted in environmental pollution, harmful impacts on beneficial microorganisms, and the emergence of new pathogens [11]. Therefore, urgent efforts are required for the sustainable development of the agriculture system to address biotic stresses and increase food production.

Plant disease resistance is typically categorized into major resistance (qualitative) and partial resistance (quantitative) [12,13]. Major resistance in plants relies on the presence of resistance genes (*R*), which encode intracellular immune receptors such as nucleotide-binding leucine-rich repeats (NLRs) and immune receptors like receptor-like kinases. These cellular immune receptors detect specific avirulence (*Avr*) proteins/cognate effectors or conserved pathogenic molecules either directly or indirectly [14]. Consequently, most *R* genes confer pathogen race-specific "gene-for-gene resistance," which can be easily disrupted, as pathogens rapidly evolve to mutate the cognate *Avr* genes to escape host recognition [15]. In contrast, partial resistance is considered broad-spectrum and long-term resistance against numerous races of pathogens, controlled by quantitative trait loci (QTL) [16]. Crop improvement programs based on plant resistance genes/QTL need to be optimized and significantly studied to overcome the existing challenges posed by phytopathogens. The only feasible approach to address this alarming situation is to deploy innovative and advanced strategies or identify resistance mechanisms to combat biotic stresses. In recent decades, advancements in biotechnology have facilitated the understanding of plant-pathogen interactions and explored physiological and molecular defense mechanisms in plants to confer resistance against pathogens. For example, recent studies have concluded that the plant growth hormone salicylic acid (SA) activates systemic acquired resistance and regulates stomatal closure *via* the cell-specific transcription factor NTM1-LIKE 9 (NTL9) upon pathogen attack [17,18]. However, despite this progress in understanding disease resistance mechanisms, critical knowledge about plant-pathogen interactions remains incomplete. Exploring these gaps is crucial to further elucidate modern genetic engineering approaches aimed at revolutionizing crop disease resistance in agricultural systems.

The rapid expansion of genome-engineering techniques has enabled the investigation of the molecular basis of plant-pathogen interactions. Genome-engineering approaches have allowed us to explore new functions or enhance existing ones in crop plants [19,20]. Recently, targeting *R*-genes-mediated pathogen resistance using CRISPR-Cas9 has provided high-yield crop varieties and durable disease resistance against pathogens [21]. Liu et al. [22] reported that knocking out the *GmTAP1* susceptibility gene in *Glycine max* enhanced resistance against *Phytophthora sojae* compared to wild-type plants. In another study, Zhou et al. [23] created targeted mutations in the *ERF922* gene and observed strong resistance against bacterial blight disease in mutant rice plants compared to non-mutated plants. Given these facts, it is expected that *R* gene-based genome engineering is more powerful, cost-effective, and rapid than natural evolution. In this article, we summarize the progress made in the current understanding of pathogen resistance mechanisms, their implications for the agriculture sector, and the prospects of CRISPR-mediated genome engineering of *R* genes to improve plant resistance against different pathogens. Moreover, new strategies for improving durable disease resistance in crops against emerging pathogens are also proposed.

## 2. Host-Based Factors Affecting Pathogen-Intrusion

### 2.1. Immune Attenuation

The distribution of energy between defense and growth needs constant fine-tuning of the signaling process, including the immediate attenuation and activation of processes that significantly overlap. Rapid activation and engagement of broad immune signaling processes, such as mitogen-activated protein kinases (MAPK), are required against pathogen resistance following pathogen perception [24,25]. The MAPK cascade, one of the best-known immune signaling systems, also plays a crucial role in this process. In *Arabidopsis thaliana*, signaling facilitated by MAPK3/6, which triggers its own inhibitory process, provides a clear illustration of immune attenuation [26]. In an elegant and comprehensive analysis of MAPK phosphatases 1 (MKP1) dynamic activity, phosphorylation of

MKP1 by MAPK6 is saturated for approximately 10 minutes after pathogen-associated molecular patterns (PAMP) treatment, leading to stabilization and elevation of MAPK1 protein levels [27]. Besides MAPKs, MKPs might dephosphorylate various substrates involved in immune signaling, as evidenced by the fact that MKP1 regulates thousands of MKP6-independent pro-immune transcriptions within 90 minutes following flg22 elicitation in *A. thaliana* [28]. Furthermore, in line with the MKP1 function as a broad regulator of immune attenuation, previous studies have shown that MKP1 act as a negative regulator in defense against hemi-biotrophic pathogens (e.g. *Pseudomonas syringae*) in *A. thaliana* and biotrophic pathogens (e.g. *Ralstonia solanacearum*) in tomato [29].

Other than MKPs, protein phosphatases (i.e. PP2A/Cs) play a substantial role in reducing kinase activity during immune signaling, contributing to immune attenuation [30]. For instance, Jagodzick et al. [31] reported that groups of PP2Cs such as Hal1/2/3 interact with MAPK3/6 and inactivate flg22-mediated jasmonic acid (JA) signaling, a crucial virulence mechanism used by pathogens to control immune signaling in plants. The dephosphorylation of MAPK4/6 by Arabidopsis AP2C1 modulates SA and JA-associated immune signaling. In another study, Guo et al. [32] reported that protein phosphatase GhAP2C1 interacts with GhMPK4 and attenuates the immune response to enhance resistance against *Fusarium oxysporum* in cotton. Other kinases, such as pattern-triggered immunity (PTI) signaling regulators BAK1, CPK6, and BIK1, also modulate the activation of PP2A/Cs under biotic stress in plants [33]. Further exploration of the complex network of molecular responses mediated by the plant immune attenuation system can elucidate these mechanisms to develop robust strategies for long-term resistance against pathogens.

## 2.2. Developmental Stage

Plants experience dynamic changes in abiotic and biotic conditions throughout their life cycle, developing unique ecological niches for host-plant interactions. The developmental stage of growth and chronological age of a plant are significantly correlated with the strength of the plant immune system [34,35]. Immune signaling becomes more robust from early developmental stage to the reproductive period; thereafter, the strength of the immune system decreases due to host senescence [36]. A recent eco-genetic study showed two approaches adopted by the Arabidopsis natural population to enhance pathogen resistance: a shortened vegetative stage to promote fast reproduction and prevent pathogen infection and death, or a prolongation of the vegetative stage to obtain more energy for the development of a robust immune [35,37]. The strength of the immune system rises from early to late-developed organs due to the spatial scale process. For example, when rice plants were infected with *Xanthomonas oryzae* pv. *oryzae*, low disease symptoms were observed in adult leaves compared to juvenile leaves [38]. In another study, cauline leaves, adult rosettes, and juvenile rosettes from 8-week-old Arabidopsis plants showed variable resistance against *Sclerotinia sclerotiorum* [39]. Similar results were observed in tobacco plants inoculated with the *S. sclerotiorum*.

Moreover, the age-related robustness of the immune system depends on the functions of essential phytohormone signaling components, as evidenced by decreased resistance in cauline and adult leaves of hormone biosynthesis mutants *abab1* (abscisic acid), *jar1* (jasmonic acid), and *sid1* (salicylic acid) compared to control plants [40]. However, the comprehensive molecular basis of developmental stage-associated host resistance remains unclear, and further studies are required to explore the underlying mechanisms of developmental stage-associated host resistance against pathogens.

## 3. Underlying Mechanisms to Counter Pathogen Attack

### 3.1. Physiological Mechanisms

#### 3.1.1. Stomatal Immunity

Plants have developed sophisticated mechanisms to recognize microbial infections and prevent pathogen intrusion through controlled stomatal regulation. Numerous studies have investigated the role of stomata in plant innate immunity in pathogen resistance [41,42]. Stomata serves as the first



line of defense against pathogens by regulating their opening and closing of guard cells. pathogen-associated molecular patterns (PAMPs) induce stomatal closure within 1 hour after pathogen recognition by host cells [43]. For example, wheat plants rapidly close their stomata upon detecting bacterial molecules *via* the FLS2 (flagellin sensing 2) receptor [44]. Similarly, the application of elicitors such as chitosan or oligogalacturonic acid, associated with fungal invasion, stimulates stomatal closure in Asiatic dayflower and tomato under biotic stress condition [45], while a bacterial phytotoxin, syringomycin, induces stomatal closure in broad bean [46].

Stomatal closure is regulated by various pathways involving functional and regulatory components, including receptors, ion channels, secondary messengers, phosphatases, and protein kinases [47]. The elevated levels of SA following pathogen invasion stimulate the generation of secondary messenger ions such as  $\text{Ca}^{2+}$ , NO, and reactive oxygen species (ROS) [48]. These secondary ion messengers further activate the SLAC1 (anion) and  $\text{K}^+$  (potassium) ion channels to facilitate stomatal closure [49]. Moreover, abscisic acid (ABA) plays a vital role in promoting stomatal closure during pathogen invasion [50].

However, prolonged stomatal closure can reduce transpiration and photosynthesis, creating an aqueous apoplast that promotes pathogen colonization. Plant genomes encode thousands of peptides that regulate reproduction, development, and long- and short-distance signaling in plants [51,52]. Peptides such as PLANT SCREW UNRESPONSIVE RECEPTOR (NUT) and SMALL PHYTOCYTOKINES REGULATING DEFENSE AND WATER LOSS (SCREWs) secreted by plants regulate PAMP- and ABA-induced stomatal closure. SCREWs, sensed by NUT, function as immunoregulatory phytocytokines and recruit the SOMATIC EMBRYOGENESIS RECEPTOR-LIKE KINASE (SERK) co-receptor to modulate immune signaling. SCREWs stimulate NUT-dependent phosphorylation of ABI1 and ABI2, resulting in reduced activity of S-type ion channels and increased activity of ABI1 towards PAMP- and OST1-induced stomatal closure. Following initiation by pathogen infection and dehydration, SCREW-NUT signaling promotes apoplastic water loss and disrupts the pathogen-rich aqueous environment to prevent colonization [53].

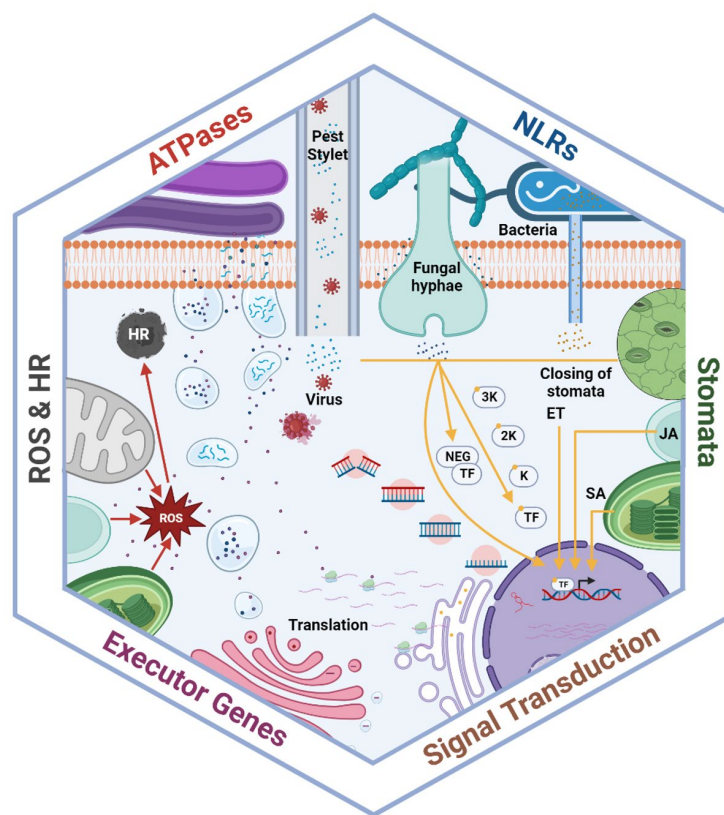
### 3.1.2. Hypersensitive Response, Reactive Oxygen Species Burst, and cell Wall Modifications

Hypersensitive response (HR) is the most common immune response in plants, inducing programmed cell death (PCD) at the site of pathogen infection to prevent the further spread of infection to healthy tissues. Pathogen infection stimulates peroxidase activity, leading to the production of ROS [54,55]. NADPH oxidases, particularly RBOHD, play a main role in this process by triggering a burst in apoplastic  $\text{H}_2\text{O}_2$  accumulation. RBOHD interacts with pattern recognition receptors (PRRs) and phosphorylates BIK1 to activate ROS production [56]. ROS stimulates PCD, and  $\text{H}_2\text{O}_2$  spreads to adjacent cells, initiating the production of chemicals such as glutathione to prevent oxidative damage [57,58]. In addition to triggering HR, ROS creates an unfavorable environment for pathogen reproduction and survival [59]. Oxalate oxidases and amines are also involved in ROS generation, along with NADPH oxidases and peroxidases [60]. Barley and wheat produce oxalate oxidase, known as germans, which break down oxalic acid secreted by pathogens to enhance resistance. Transgenic plants with barley and wheat oxidase genes have shown improved resistance to *S. sclerotiorum* compared to control plants [61–63].

Pathogens are required to penetrate the cell wall to enter the host plant for successful infection by overcoming the physical barriers. The plant cell wall is reinforced with various polymers at sites of pathogen attack to inhibit intrusion [64]. Silicon (Si) is the most observed polymer deposited in the cell wall, along with lignin, callose, and extensins to prevent pathogen infection [65]. This deposition is supported by the upward translocation of Si through the apoplast, followed by Si deposition in the extracellular spaces of xylem vessels and leaf epidermal cells [66]. This process forms a thick layer of Si-cuticle complex in the membrane, providing mechanical resistance and enhancing plant resilience against pathogen attack. Si also forms complexes with organic compounds in epidermal cell walls, providing further strength and reducing disease intensity [67]. Abdelrhim et al. [68] reported that the application of Si improves resistance against *Rhizoctonia solani* in wheat plants by increasing extracellular adsorption in the spongy mesophyll and air spaces of the leaf. Si-mediated modifications in the cell wall contribute to increased plant physical resilience against pathogen penetration.

### 3.1.3. Phytohormones

Plants produce a diverse array of metabolites crucial for activating defense signaling against phytopathogen attacks (Figure 1). Among these metabolites, ABA, ethylene (ET), JA, and SA emerge as pivotal signaling molecules or phytohormones responsible for mediating defense responses across various pathogen lifecycles [69,70]. SA regulates local and systemic resistance responses to biotrophic and hemibiotrophic pathogens and interacts with numerous developmental and response functions [71]. SA and MAPK cascades can act upstream of each other, with SA activating MAPK cascades and some cascades stimulating SA activity [72,73]. SA transfers signals regarding pathogen presence through a complex signaling cascade, activating transcription factors to induce the expression of defense-related genes. After initiating a signaling cascade, SA mediates the reduction of disulfide bonds within the oligomeric protein nonexpressor of pathogenesis-related genes 1 (NPR1) by thioredoxins. This reduction process facilitates the translocation of NPR1 monomers from the cytosol into the nucleus. Within the nucleus, these monomers bind to the transcription factor TGA, specifically at the TGACG binding site, and upregulate the expression of resistance genes [74,75].



**Figure 1.** Components of plant disease resistance mechanisms involved in pathogen detection, signal transduction, and defense response.

ET and JA play significant roles in conferring resistance against herbivorous insects and necrotrophic pathogens. These hormones stimulate the secretion of volatile compounds in response to caterpillar oral secretions [76]. ET synthesis increases upon perception of bacterial flagellin [77]. In the absence of ET, the F-box protein degrades the ethylene insensitive 3 (EIN3) transcription factor through proteasome and ubiquitination activity. ET inactivates the constitutive triple response1 (CTR1) protein and its receptors, reducing EIN2 and EIN3 expression and allowing upregulation of ET signaling and necrotroph resistance [78,79]. Pathogen interference also targets this pathway, with the XopD effector from *Xanthomonas euvesicatoria* bacterium desumoylating the transcription factor SIERF4 to disrupt hormone signaling, particularly inhibiting ET synthesis and resistance [80]. In addition to ET and JA, auxin and ABA are involved in plant resistance against pathogens. Stomata closure is linked to ABA signaling, regulating gas exchange, water loss, and preventing pathogen access to plant tissues [81]. Peptides can also act as plant hormones. Some studies have demonstrated

that small peptide hormones like systemin are involved in systemic herbivory response, resulting in changes in gene expression, particularly in neighboring plants not exposed to biotic stress [82,83]. This suggests that plant hormones can facilitate communication among individual plants to enhance resistance.

### 3.2. Molecular Mechanisms Underpinning R Genes

#### 3.2.1. Host Reprogramming by Passive Loss of Susceptibility

Mutations in cellular pathways represent a common strategy for host reprogramming, offering durable resistance against various pathogens. This form of susceptibility loss is typically governed by recessive traits, but sometimes dominant alleles are also involved. Genes associated with this phenomenon are termed adult plant resistance (*APR*) genes, as they confer resistance to plants in their later stages [84]. Moreover, *APR* genes commonly provide partial protection against a broad spectrum of pathogens [85]. It is important to note that the processes underlying this type of resistance are not used in adult plants, thus the term *APR* does not fully encompass this category. Furthermore, loss-of-interaction and perception-based mechanisms may specifically function in adult plants. For instance, recessive loss-of-function *mlo* (Mildew Locus O) alleles serve as key regulators of a senescence-associated loss-of-susceptibility mechanism in both monocots and dicots. *MLO* encodes a protein integral to membrane function, acting as a negative regulator of cell death under biotic stresses. Spontaneous cell death is associated with *MLO* loss-of-function alleles [86].

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Therefore, analogous to *pi21*, the generation of loss-of-function alleles from genes encoding HMA domains confers resistance to many pathogenic fungi in different plant species. Similarly, the dominant *R* gene *Lr67* in wheat provides partial adult resistance to stem rust, leaf rust, and powdery mildew, primarily due to mutations in a hexose transporter that differs from the susceptible allele by two amino acids. The heterodimerization of *Lr67* with the susceptible allele product exhibits dominant negative effects, resulting in decreased glucose uptake and leaf tip necrosis [93,94]. The resistance conferred by these genes depends on the deregulation of early defense responses.

#### 3.2.2. Disrupting Interaction with Host Key Targets

The disrupting interaction with key host susceptibility factors is a common mechanism underlying recessive *R* genes. Indeed, various identified *R* genes are involved in loss-of-interaction mechanisms to confer resistance against viruses [95]. Most of the known *R* genes act against potyviruses and encode 4E or 4G family mutant translation initiation factors, which are unable to interact with viral transcripts cap structures, thereby imparting resistance to potyviruses [96]. Moreover, about one-third of the protective *R* genes involved in resistance against bacterial blight disease are recessively inherited, and disrupting interaction with key host targets appears to be an underlying mechanism [97]. A recessive mutation in the promoter area of the *xa27* allele prevents

TALEAvrXa27 (Transcription activator-like effectors) from manipulation, resulting in the loss of susceptibility [98]. Similarly, a mutation in a single amino acid of the recessive *xa5* gene encoding Ila OsTFIIA $\gamma$ 5 (gamma subunit of a transcription factor) restricts bacterial movement and confers resistance to different *X. oryzae* strains in the adult plant [99]. OsTFIIA $\gamma$ 5 interacts directly with TALEs to complete their activity [100]. The mutation in *Xa5* seems to affect the Xa5-TALEs interaction, thus showing a varying degree of resistance against many pathovars of *X. oryzae* [101,102].

### 3.2.3. NLRs Activation by Direct Intracellular Recognition of Effectors

The direct recognition of effectors is not limited to the cell surface, as various effectors have been reported to directly interact with nucleotide-binding leucine-rich repeat proteins (NLRs) to stimulate a defense response against pathogens [103]. For example, an effector of *Hyaloperonospora Arabidopsis thaliana* recognized1 (ATR1) interacts directly with the NLR *Peronospora parasitica*1 (RPP1), resulting in its recognition [104]. Numerous RPP1 alleles have different perceptions specific to ATR1 alleles, and the LRRs of RPP1 mediate this specificity [105]. Similarly, another effector, AVR1567 from *Melampsora lini*, binds directly to its cognate receptors L5, L6, and L7 NLRs, encoded by allelic genes [106,107]. These receptors recognize AvrL variants differently, and the LRR domain of the NLR determines this specificity [108,109]. Interestingly, cooperative polymorphism in other NLR domains also influences the perception of effectors, showing a perception mechanism in which intramolecular interactions compete with effector binding. The L5, L6, and L7 effectors exist in an “off” and “on” equilibrium state, and the binding of effectors triggers immune signaling by stabilizing them to the “on” state [107,110]. This equilibrium model might have a wider range of applications in NLR signaling. Indeed, 21 amino acid peptides from the viral movement protein (NSm21) are directly recognized by the NLR Sw-5b, and it has been explored that NSm21 binding disrupts the interaction between NB-ARC and the leucine-rich repeats (LRR) domain, triggering perception [111].

Variants of allelic effectors are perceived by allelic NLR-encoding genes in the case of L5/6/7 and RPP1. However, the perception of homologous effector proteins by homologous and/or allelic NLRs is not constant. For instance, barley and rice both have similar NLRs located within the *R* gene cluster. These NLRs can recognize distinct effectors from *Blumeria graminis* and *M. oryzae*, regardless of the differences in their genetic sequences [112,113]. Moreover, potato orthologs of two distinct NLR-encoding genes in tomato L2, which recognize a fungal effector, and Sw-5b, a viral effector, can also identify effector proteins from oomycetes [114,115]. The exact molecular mechanism by which highly similar NLRs detect sequence-unrelated effectors from different pathogens is still unraveled. In several cases, the C-terminal LRR region of the NLR has the specificity-determining region, while a mutation in a different location than the NLR is sufficient to alter the specificity [116,117]. Minor variations across various regions of the NLR appear to prompt its recognition of unrelated effectors. Moreover, the effectors might evolve distinct specificity to sequence-unrelated effectors by adopting a similar fold. Indeed, gaining a structural understanding of how these NLRs bind to effectors could offer more insights into the molecular mechanisms of direct perception [118,119].

### 3.2.4. Active Loss of Susceptibility

Active loss-of-susceptibility mechanisms encode host proteins that disarm pathogens by disrupting their lifecycle. These mechanisms are diverse and provide resistance against various pathogens. The active loss of susceptibility mechanisms triggers the generation of danger-associated molecular patterns (DAMPs) and PAMPs after pathogen recognition [120]. For example, the first cloned *R* gene, *Hm1* encodes an NADPH-dependent reductase usually involved in detoxifying HC toxin in maize (Table 1) [121]. *Cochliobolus carbonum* race 1 (CCR1) is a key virulence factor of HC, causing ear mold and leaf light in maize. *Hm1* orthologs exist in barley and the grass family and such orthologs play a significant role in providing non-host resistance against CCR1 [118]. Numerous active loss-of-susceptibility mechanisms are employed to develop resistance against viruses in plants. For instance, the *Tm-2* gene product of tomato provides resistance against the Tomato mosaic virus



and inhibits replication by binding to replication proteins [119]. Furthermore, the resistance genes *Ty-1/Ty-3* in wild tomato encode  $\gamma$ -clade RNA-directed RNA polymerases. These enzymes initiate RNA-directed DNA methylation, offering protection against single-strand DNA geminiviruses [122].

3.2.5. TAL Effector-Dependent Expression of Executor Genes

Executor genes comprise a new class of *R* genes that are transcriptionally activated by TALEs produced by *Xanthomonas* species, conferring resistance against *Xanthomonas* strains carrying these TALEs. The TALEs secreted by *Xanthomonas* species act as important virulent factors that regulate the expression of susceptibility (*S*) genes for disease development [123,124]. Executor genes function as promoter traps, stimulating the transcription of immunity-related genes. The promoter of executor genes acts as a decoy, duplicating the promoter regions of susceptibility factors, thus activating the defense response [125]. Various executor genes have been identified and cloned in different plant species to confer resistance against different phytopathogens, such as in rice *Xa10* [126], *Xa23* [127], *Xa27* [128], in pepper *Bs4C-R* [129], and *Bs3/Bs3-E* [130]. Previously reported executor genes (*Bs4C-R*, *Xa10*, *Xa23*, and *Xa27*) either encode a protein with many putative transmembrane domains or encode a protein with catalytic activity for flavin monooxygenase (*Bs3* and *Bs3-E*). However, an improved understanding of the specificity of DNA binding to TALEs provides more insights into developing immunity against various *Xanthomonas* strains [131,132]. This approach was also employed to engineer RipTALs for resistance development against *R. solanacearum* in tomatoes [133].

**Table 1.** List of cloned *R* genes against different disease in plants.

Crop specie	Gene	Protein type	Disease	Pathogen	Reference
Barley	<i>Stb6</i>	Receptor kinase	Septoria tritici blotch	<i>Zymoseptoria tritici</i>	[198]
	<i>Mla1</i>	NB-LRR	Powdery mildew	<i>Blumeria graminis</i>	[199]
	<i>Mla6</i>	NB-LRR	Powdery mildew	<i>B. graminis</i>	[200]
	<i>Rpg1</i>	Protein kinase	Stem rust	<i>Puccinia graminis</i>	[201]
Wheat	<i>Pm3</i>	NB-LRR	Powdery mildew	<i>B. gramini</i>	[202]
	<i>Lr10</i>	NB-LRR	Leaf rust	<i>P. triticina</i>	[83]
	<i>Lr21</i>	NB-LRR	Leaf rust	<i>P. triticina</i>	[202]
Maize	<i>ZmTrxh</i>	H-type thioredoxin	Lethal necrosis	<i>Sugarcane mosaic virus</i>	[203]
	<i>Rp1-D</i>	NB-LRR	Leaf rust	<i>Puccinia sorghi</i>	[204]
	<i>Rxo1</i>	NB-LRR	Bacterial streak	<i>Xanthomonas oryzae</i>	[205]
	<i>Hm1</i>	HC toxin reductase	corn leaf blight	<i>Cochliobolus carbonum</i>	[121]
	<i>Hm2</i>	HC toxin reductase	corn leaf blight	<i>C. carbonum</i>	[206]
	<i>Rp3</i>	NB-LRR	Leaf rust	<i>Puccinia sorghi</i>	[57]
	<i>qRfg1</i>	CCT domain gene	Gibberella stalk rot	<i>Fusarium graminearum</i>	[208]
	<i>qMdr9.02</i>	Lignin biosynthesis	Multiple	Multiple	[209]
	<i>Piz-t</i>	NB-LRR	Rice blast	<i>Magnaporthe oryzae</i>	[210]
	<i>Pi-ta</i>	NB-LRR	Rice blast	<i>M. oryzae</i>	[211]
Rice	<i>Pi-b</i>	NB-LRR	Rice blast	<i>M. oryzae</i>	[212]

	<i>Pi-d2</i>	B-lectin receptor kinase	Rice blast	<i>M. oryzae</i>	[213]
	<i>Pi9</i>	NB-LRR	Rice blast	<i>M. oryzae</i>	[214]
	<i>RGA 5</i>	NB-LRR	Rice blast	<i>M. oryzae</i>	[215]
	<i>Xa1</i>	NB-LRR	Bacterial blight	<i>X. oryzae</i>	[216]
	<i>Xa5</i>	TFIIA Transcription factor	Bacterial blight	<i>X. oryzae</i>	[217]
	<i>Xa7</i>	Executer R protein	Bacterial blight	<i>X. oryzae</i>	[218]
	<i>Xa10</i>	Executer R protein	Bacterial blight	<i>X. oryzae</i>	[126]
	<i>Xa21</i>	Receptor kinase	Bacterial blight	<i>X. oryzae</i>	[219]
	<i>Xa23</i>	Executer R protein	Bacterial blight	<i>X. oryzae</i>	[127]
	<i>Xa26</i>	Receptor kinase	Bacterial blight	<i>X. oryzae</i>	[220]
	<i>Xa27</i>	No homolog	Bacterial blight	<i>X. oryzae</i>	[128]
<i>Arabidopsis thaliana</i>	<i>FLS2</i>	NB-LRR	Necrosis	<i>Pseudomonas syringae</i>	[221]
	<i>RPM1</i>	NB-LRR	Necrosis	<i>Peronospora parasitica</i>	[222]
	<i>RSP2</i>	NB-LRR	Necrosis	<i>P. syringae</i>	[223]
<b>Tomato</b>	<i>Cf-2</i>	NB-LRR	Leaf mold	<i>Cladosporium fulvum</i>	[159]
	<i>Prf</i>	NB-LRR	Necrosis	<i>P. syringae</i>	[157]

3.3. Metagenomic Dynamics

Plants harbor a diverse assembly of microbial communities, which colonize the roots during the life cycle of host plants. These host-associated microbes confer beneficial traits to plants, such as disease suppression, nutrient uptake, and promotion of plant growth [134,135]. Moreover, microbes trigger defense mechanisms that enhance the resilience of host plants to pathogens, significantly increasing disease-combating efficiency [136]. Microbiomes also enhance the defense capabilities of plants by disrupting interactions between plants and pathogens, to increase disease resistance. Bacterial antagonists belonging to genera such as *Enterobacter*, *Comamonas*, *Pantoea*, and *Microbacterium* have shown significant biocontrol against rice blast disease and have stimulated the expression of genes involved in defense responses, such as *OsPAD4*, *OsCEBiP*, *OsEDS1*, and *OsCERK1* in rice seedlings [137]. Similarly, root-associated microbes like *Pantoea* sp. EA106 and *Pseudomonas* sp. EA105 induces disease suppression in *M. oryzae*-inoculated rice plants by triggering ET and JA-induced systematic resistance [138]. However, advances in molecular biology have led to the development of omics techniques, such as metagenomics, which have recently gained importance in exploring the diversity of plant-microbe interactions. Metagenomics has the potential to target numerous unique signature loci in pathogen-affected plants. This approach has already been utilized in agriculture to identify novel genes, enzymes, and microbial communities involved in disease suppression [135,139].

A recent study conducted by Llontop et al. [140] found genes and key bacterial taxa, including 33,000 archaeal and bacterial species, involved in the suppression of fungal pathogens causing root diseases. Similarly, Mendes et al. [141] conducted a metagenomic analysis and showed that *Fusarium*

*oxysporum* (Fox) infection led to increased microbial diversity, network complexity, and a higher proportion of the genera *Flavobacterium*, *Bacillus*, and *Dyadobacter* in the rhizosphere of the fox-resistant cultivar compared to the fox-susceptible cultivar. Moreover, unique functional traits such as the biosynthesis of antifungal genes, rhamnolipids, and phenazines, as well as protein secretion systems, were dominant in the rhizobia community of *P. vulgaris*. In another study, a comparative metagenomic analysis of resistant and susceptible varieties of tomatoes to *R. solanacearum* revealed the abundant presence of *Flavobacterium* in the resistant variety. When rhizosphere microbiota from the resistant variety were transplanted to the susceptible variety, reduced disease symptoms were observed compared to non-treated plants Kwak et al. [142]. These studies indicate that microbiome analysis through metagenomics provides a paradigm shift and insights into deciphering the role of the microbial community in protecting against different pathogens. Moreover, the knowledge gained from these aspects through metagenomics could be utilized to engineer rhizosphere or microbial consortia to enhance plant potential to withstand biotic stresses.

#### 4. Strategies to Exploit Innate Immune Responses of the Host for Disease Resistance

##### 4.1. Introgression of *R* Genes from Wild Species

The decline in crop diversity has increased the risk of modern crops to pathogen attacks, primarily due to the continuous pursuit of monoculture for high productivity [143]. Landraces and wild species serve as significant resources for novel *R* genes that can be introduced into modern varieties to combat emerging races of pathogens [144]. Hence, there is an imperative need to identify new *R* genes/alleles and introgressed them into modern varieties to obtain resistance. Indeed, various *R* genes, such as *Xa21*, *Xa23*, *Xa27*, *Yr36*, *CcRpp1*, and *Fhb7*, have been introgressed from landraces or wild species of plants into modern varieties to confer resistance against pathogens [127,128,145]. The *Fhb7* gene, derived from wild relatives of wheat, confers resistance against *Fusarium* head blight [146], while *CcRpp1*, introgressed from a wild pigeon pea, showed strong resistance against soybean rust [147]. Similarly, in another study, the *Rph* gene was introgressed from wild barley carrying resistance to the leaf rust pathogen (*Puccinia hordei*) [148]. However, an efficient field trial platform is required to identify effective elite alleles and *R* genes involved in disease resistance for breeding programs. Natural-based selection for severely damaging crop pathogens must be developed for widespread screening of germplasm resources to develop resistance. Therefore, plants under high-pressure selection in fields are exposed to continuous infection by pathogens throughout plant growth to identify new resistance genes. Similarly, pigm-mediated resistance was confirmed using nursery trials in different locations over multiple years, inoculating with various isolates [149,150].

##### 4.2. Identification and Acceleration of *R* Gene Cloning

The identification and cloning of *R* genes are expensive and slow processes, primarily due to the preparation of libraries and artificial bacterial chromosomes. However, in recent years, advances in bioinformatics and genome sequencing technology have enabled the exploration of genomic regions linked with complex traits [144]. Moreover, high-throughput-based genotyping facilitates the detection of QTLs and genes associated with pathogen resilience. Mapping-by-sequencing is also gaining importance in identifying and cloning novel *R* genes in plants [151]. The genetic architecture of *R* genes in important crops has been identified through genome-wide association studies (GWAS) [152]. For example, *R* genes against rice blast disease, such as *LABR\_64* and the partial resistance gene *LABR12*, have been identified using GWAS analysis [153,154]. Similarly, scald resistance genes, including *Rrs1*, *Rrs2*, *Rrs4*, *Rrs12*, *Rrs13*, *Rrs14*, *Rrs15*, *Rrs17*, and *Rsr18*, have been identified in barley germplasm across different chromosomes using GWAS and mapped through different molecular markers [155–157].

Association genetics combined with gene enrichment sequencing (AgRenSeq) is another powerful tool for identifying NLR-like genes from landraces or wild species. AgRenSeq, which combines RenSeq with association mapping to achieve pan-genome variation in diverse crop germplasm, has been used to clone *R* genes such as *SrTA1662*, *Sr33*, and *Sr45* in wheat. Mut-RenSeq,

a technique that combines mutagenesis and RenSeq, was used to identify and isolate two resistance genes of stem rust, namely *Sr45* and *Sr22*, in wheat [158]. Similarly, MutChromSeq combines chromosome flow sorting, EMS mutagenesis, and high-throughput sequencing to identify induced mutations in plants by comparing them with parental chromosomes [159]. Gao et al. [160] reported a new method targeting chromosome-based cloning by long-range assembly (TACCA). TACCA assembles complex genomes by combining Chicago long-range linkage with chromosome flow sorting. This technique has been employed to clone the *Lr22a* leaf rust-resistant gene in 4 months using ethyl methylsulfonate and marker information in wheat plants.

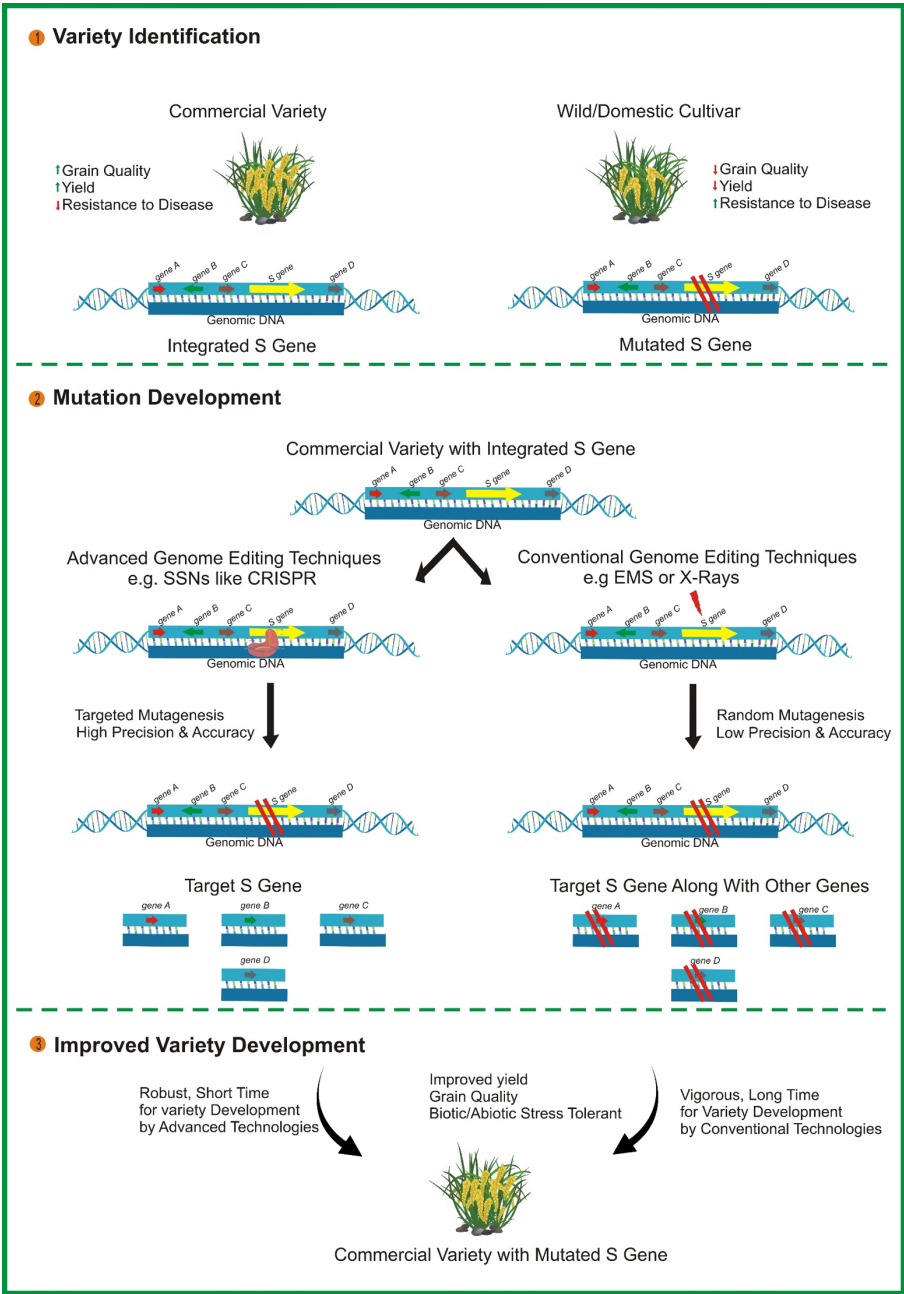
#### 4.3. CRISPR-Cas9-Mediated Genome Engineering to Confer Disease Resistance

Conventional breeding plays a crucial role in improving plant resistance to pathogens, usually involving the growth and screening of large crop populations over multiple generations. However, identifying plants with the desired traits from such a vast population is labor-intensive and time-consuming [161]. The rapid advancement of genome engineering approaches in recent decades has enabled the modification of numerous components of the plant immune system to achieve long-term resistance against pathogens. Zinc finger nucleases (ZFNs), transcription-activator-like effector nucleases (TALENs), and CRISPR (clustered regularly interspaced short palindromic repeats)/associated Cas9 protein are widely used approaches for generating site-specific genetic mutations and developing disease-resistant plants [162]. Both ZFNs and TALENs rely on chimeric proteins consisting of non-specific cleavage nucleases and sequence-specific DNA binding [163,164]. However, their applications present certain challenges such as high cost, complex construction, and high off-target rates, which hinder their widespread use in agricultural research. In contrast, CRISPR/Cas9 is a technically simpler and time-saving method that can be deployed for genome engineering, offering promising prospects for improving plant disease resistance against dominant phytopathogens [161,165].

CRISPR-Cas9 has been extensively utilized for targeted mutagenesis in host plants to confer disease resistance in important agricultural crops [166]. For instance, CRISPR-Cas9 was successfully employed to confer resistance in wheat against powdery mildews by simultaneously targeting three MLO homologs, namely TAMLO-A, -B, and -D [167]. In another study, the knockout of the *OsERF922* gene increased resistance against blast fungal pathogens in rice [168]. Moreover, CRISPR/Cas9-enabled mutagenesis of the eukaryotic translation initiation factor 4E (eIF4E) has been shown to enhance resistance to potyviruses in *A. thaliana* [169] and cucumber [170]. Similarly, targeted mutagenesis has also been employed to confer resistance against *Phytophthora infestans* by CRISPR/Cas9-mediated engineering of *TaNFLX1*, reducing post-infection pathogen proliferation in wheat [171]. In *Brassica napus*, the knockout of the *BnWRKY70* gene increases host resistance against *S. sclerotiorum* [22].

CRISPR/Cas9 also offers significant potential for engineering S genes, which are essential for facilitating the infectious process of pathogens (see Figure 2). Disabling plant S genes through genome editing is a novel approach to confer broad-spectrum disease resistance in various economically important crops [172]. For instance, eIF4E is required for the cellular infection cycle of potyviruses. The 5'-terminal capped protein interacts with eIF4E to initiate the translation of viral proteins. CRISPR/Cas9-enabled mutagenesis of eIF4E has led to improved resistance to potyviruses in cassava [173]. Similarly, Mlo encodes a membrane-associated protein essential for the penetration of powdery mildew (PM) fungus into host epidermal cells. Mutation in Mlo through CRISPR-Cas9 has mediated resistance in tomato [174] and wheat [175] via a non-transgenic system. Furthermore, a mutation introduced in DOWNY MILDEW RESISTANCE 6 (DMR6) through CRISPR/Cas9 in grapevines has conferred increased resistance to downy mildew disease [176]. Collectively, the studies illustrate the outstanding performance of CRISPR/Cas9 in developing disease-resistant crop varieties. Despite the remarkable achievements to date, challenges such as off-target effects remain to be addressed. However, potential future avenues for this technology in terms of design and application could be considered. Further identification of S genes in various plant species will pave the way for the long-term development of disease resistance using CRISPR-Cas9 technology.





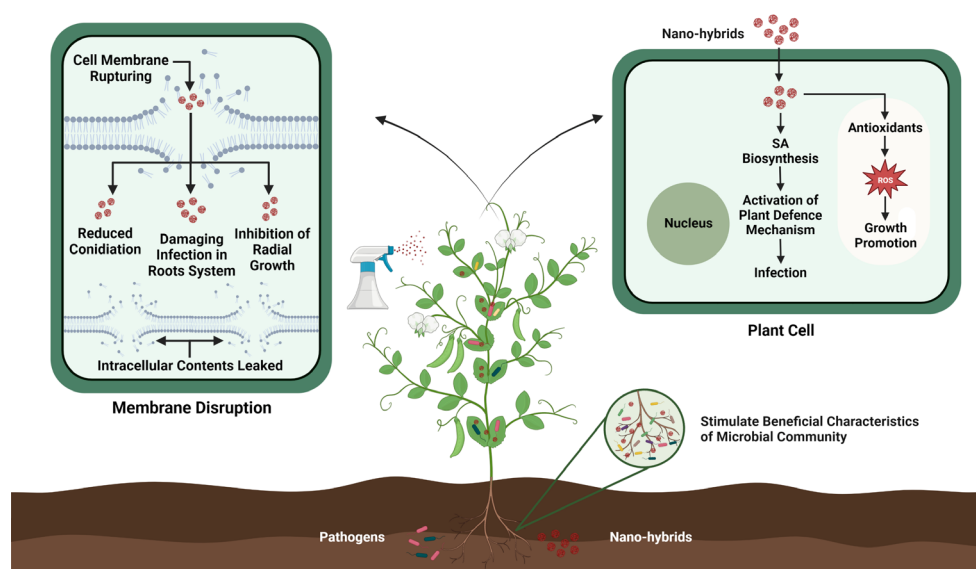
**Figure 2.** illustration of development of disease-resistant variety in plants by targeting susceptibility (S) gene/s via CRISPR/Cas9 system.

4.4. Nanohybrid-Induced Plant Disease Resistance

Traditional techniques such as crop cultivation management and plant breeding provide a solution to potentially ensure food security and safety, as well as to help plants cope with various stresses. However, these methods cannot effectively address the issues due to long process. The only practical solution to overcome this alarming situation is to employ innovative and advanced strategies or develop stress-resilient varieties to combat environmental challenges. The emergence of precise and modern genome engineering techniques, such as CRISPR-Cas9, has significantly increased the versatility of gene editing due to its superior efficacy in inducing targeted mutagenesis in the target genome [162,165]. The successful implementation of CRISPR/Cas9 for improving various agronomically important traits in diverse plant species reveals that this technology could become invaluable for crop improvement. However, these advanced genetic engineering techniques still face various challenges, including modularity, epigenetics, high complexity, standardization, difficulties

in characterization, and the risk of accidental release into wild species. Moreover, genetic modification is an irreversible process, raising significant social concerns [177,178].

Nanohybrids, with their valuable and unique properties, have emerged as a stimulating branch of nanotechnology with a vast variety of applications in the agriculture sector. These nanohybrids endow augmented new properties such as tolerance against environmental stresses, artificial photosynthesis, and improved plant innate immunity [179,180]. Moreover, the advent of nanohybrids has also revolutionized the field of plant genetic engineering by enhancing plant resistance against pathogens without causing any harmful effects on the environment (see Figure 3). For example, silver nitrate coated with titanate nanotubes (AgTNTs) significantly inactivates the replication of *Botrytis cinerea* through the photoinactivation method. The sharp morphology and cytotoxicity of AgTNT trigger ROS production, which inhibits the further spread of conidia [181]. Similarly, Sidhu et al. [182] reported that MgO-sepiolite nanohybrids showed effective antifungal activity against devastating pathogens such as *F. fujikuroi*, and *F. verticillioides*, and *Bipolaris oryzae* compared to MgO NPs. MgO-sepiolite causes extensive damage to hyphae by breaking the cell wall and internal damage. In another study, Ranpariya et al. [183] synthesized silver-platinum nanohybrids (AgPtNHs) using *Dioscorea bulbifera* tuber extract and found that AgPtNHs exhibit strong antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, as well as significantly inhibit biofilm formation.



**Figure 3.** Mechanistic action of nanohybrids induced pathogen resistance in plants.

Given the remarkable structural diversity and composition of advanced synthetic materials, nanohybrid-based genome engineering is anticipated to be more powerful, cost-effective, and rapid compared to traditional genetic engineering or natural evolution. However, as information on nanohybrid-based genome engineering remains limited, further research in this area is necessary to deepen our understanding and strengthen our knowledge.

## 5. Challenges and Future Directions

Scientific communities and public institutions are investing considerable financial and human resources into the development of disease-resistant crops to sustain agricultural production. However, a considerable number of technical challenges are still to be solved.

### 5.1. Food Safety Issues

Agricultural production serves as the cornerstone of the modern economy. Both traditional and recently developed gene engineering methods show promise in addressing food security issues. However, concerns have arisen about food safety with the adoption of modern genetic engineering

approaches [184]. Emphasizing food safety over the incorporation of new properties and traits is crucial. However, concerns exist regarding the ecological hazards and potential health risks associated with genetically modified crops intended for human consumption [178]. For instance, 'Starlink' maize, engineered to express Cry9c, was approved for industrial use and animal feed in the USA but not for human consumption due to elevated protein levels and potential immune system interactions [185]. Subsequently, Aventis discontinued 'Starlink' due to the detection of Cry protein residues in food products [186]. Moreover, certain studies have suggested potential health hazards such as chronic kidney diseases, increased tumor incidences, female mortality, and necrosis in male rats fed with transgenic maize known as 'Seralini' [187]. However, this study faced criticism for inappropriate statistical analysis and flawed experimental design, resulting in subsequent retraction. The research group later republished the study in 2014 with an extended format, underscoring the need for long-term feeding experiments to assess the safety of modified crops [188]. Further concerns have been raised about the potential horizontal transfer of antibiotic resistance marker genes to humans and gut bacteria in animals [189].

Pollen-mediated transfer of transgenes from transgenic crops to wild cultivars has been documented in various crops, including rice [190,191]. The introgression of transgenes from transgenic crops to conventional cultivars raises concerns about biodiversity loss and gene flow to weeds or their relatives, potentially leading to adverse effects such as the emergence of herbicide-resistant weeds and new weed species. For instance, 16 glyphosate-resistant weed species have been identified, developed due to modern engineering approaches [192]. *Amaranthus tuberculatus* and *A. palmeri* are among the most resistant weeds, significantly impacting the global economy [193]. Therefore, the development of proper testing methods is imperative to evaluate the safety of genetically modified crops and sustain the agricultural food production system in the future.

### 5.2. Nano Vehicle-Based Gene Delivery to Enhance Disease Resistance Traits

In recent years, CRISPR-Cas9 technology has made major revolutions in plant genome editing, enabling efficient and precise editing. However, some challenges are present about gene delivery methods. Conventional delivery techniques, such as *Agrobacterium tumefaciens*, protoplast transformation, biolistic, and liposome-mediated methods, have limitations including low transformation efficiencies, tissue damage, host-range restrictions, and complex protocols [194]. The rapid advancement of nanotechnology in recent decades has redirected plant genetic engineering towards nanoparticle-mediated gene transformation to overcome these challenges. Nanoparticles offer promising solutions due to their unique physicochemical properties, tunable size, and ability to penetrate biological barriers, thereby inducing desirable traits such as disease and pest resistance in plants [195]. For instance, Hajiahmadi et al. [196] used silicon nanoparticles (SiNPs) for delivering the cryIAb gene-containing plasmid into tomato plants by injecting the solution into the abaxial surface of tomato leaves. Subsequent bioassays and molecular analyses confirmed the expression of *cryIAb*, resulting in increased resistance of tomato plants against *Tuta absoluta*. Similarly, chitosan nanoparticles (Chitosan NPs) have been shown to enhance cargo delivery, leading to a significant increase in protection or durable resistance against pearl millet downy mildew in pearl millet [197].

### 5.3. Public Acceptance and Awareness

Modern agricultural practices have led to environmental degradation, land pollution, and ecosystem disruption, aggravated by the extensive use of chemical fertilizers. This unsustainable scenario in the food and agriculture sector requires innovative solutions. Recent research has unveiled the potential of nanohybrids to enhance disease resistance, improve agricultural inputs, and address agriculture-related challenges, thereby promoting plant resistance and food security. The prospective use of nanoscale agrochemicals, such as nanohybrid-based fertilizers, has transformed traditional agricultural practices, making them more sustainable and efficient. However, the application of nano-products in real-life scenarios raises concerns about exposure levels and potential toxicological effects on human health and the environment, highlighting the need for public awareness to alleviate confusion and stigmatization (from perceiving nano-products as either 'nano-

good' or 'nano-bad'). To mitigate these risks, governmental and non-governmental organizations must implement regulatory frameworks to assess the ecotoxicological effects of nano-agrochemicals prior to their use in any sector. Moreover, addressing commercial potential, implementation barriers, and policy regulations about the use of nano-agrochemicals in agriculture is imperative to ensure their safe and effective integration into agricultural practices.

## 6. Conclusions

The knowledge of plant-pathogen interactions has experienced exponential growth in the 21<sup>st</sup> century, boosted by significant advancements in computational power and the emergence of molecular technologies. From the identification of (PAMPs to the implementation of robust defense mechanisms by plants, the ongoing arms race between hosts and pathogens underscores the intricate nature of these relationships. Furthermore, with the onset of climate change and evolving agricultural practices, new pathogen strains are emerging, requiring the urgent development of sustainable agricultural systems to address these challenges. However, by delving into the molecular mechanisms underlying plant-pathogen interactions, researchers can uncover fundamental biological processes that offer promising avenues for bolstering crop resilience against diseases. Leveraging this knowledge presents opportunities to devise innovative, targeted strategies for crop protection that are both environmentally sustainable and economically viable.

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