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Integration of Genetic Resistance Mechanisms in Sustainable Crop Breeding Programs-A Review

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ABSTRACT

The integration of genetic resistance mechanisms into sustainable crop breeding programs is critical for addressing global agricultural challenges, including the increasing threats posed by pests, diseases, and climate change. Genetic resistance, which involves the use of innate plant defense mechanisms, provides an environmentally friendly alternative to chemical controls and plays a pivotal role in enhancing crop resilience. Advances in molecular biology, such as CRISPR-Cas9 gene editing and multi-omics technologies (genomics, transcriptomics, and metabolomics). have revolutionized resistance breeding, enabling the precise identification, modification, and deployment of resistance traits. These tools facilitate the development of crops with enhanced resistance to biotic and abiotic stresses while reducing yield penalties and linkage drag. Challenges such as the evolution of pathogen virulence, the breakdown of race-specific resistance genes, and the trade-offs between resistance and crop quality remain significant hurdles. Durable resistance, achieved by combining qualitative and quantitative resistance traits, offers a promising approach to mitigate these issues and delay resistance breakdown. Agroecological practices, such as crop diversification, companion planting, and organic amendments, can complement genetic resistance by reducing pathogen pressure and improving ecosystem stability. International research collaborations, such as those led by CGIAR, along with local capacity-building efforts, are essential to ensure the equitable dissemination of resistance technologies, particularly in resource-limited regions. Despite these advances, socioeconomic and regulatory barriers, including public skepticism toward genetically engineered crops and stringent approval processes for GMOs and gene-edited varieties, hinder widespread adoption. Increased investments in breeding research, streamlined regulatory frameworks, and policies promoting resistant varieties are vital to overcoming these challenges. As the global demand for food continues to rise amidst climate uncertainties, the integration of cutting-edge genetic tools, ecological principles, and collaborative efforts offers a pathway to more sustainable and resilient agricultural systems. By addressing current limitations and leveraging emerging technologies, genetic resistance can significantly contribute to global food security and the sustainability of modern farming practices.

Keywords: Genetic resistance; CRISPR-Cas9; multi-omics; quantitative resistance; durable resistance.

1. INTRODUCTION

1.1 Importance of Sustainable Agriculture and Food Security

The urgency to ensure global food security in a rapidly changing world places sustainable agriculture at the forefront of modern agricultural innovation. By 2050, the global population is projected to reach 9.7 billion, necessitating a 60% increase in food production compared to 2005 levels (Lal, 2006). The agricultural sector faces formidable challenges, including the impacts of climate change, pest and disease outbreaks, and resource degradation. Climate change, in particular, has already begun to disrupt crop yields through extreme weather droughts. events. such as floods. and heatwaves. For example, global wheat yields are

expected to decline by 6% for every 1°C rise in temperature, while maize and rice yields face similar threats. Pests and pathogens cause significant crop losses annually, with an estimated 20-40% of global productivity lost to these threats. The fall armyworm (Spodoptera frugiperda), has rapidly spread across sub-Saharan Africa, posing a major threat to maize production (Kansiime et al., 2023). Alongside these challenges, unsustainable farming practices have degraded over 25% of the world's arable land, and water scarcity affects nearly half of the global population. To combat these crises, agricultural systems must evolve to prioritize resilience and resource efficiency. Sustainable crop breeding offers a vital pathway to address these global challenges by integrating genetic innovations with ecological principles. By focusing on developing crop varieties that are resistant to both biotic stresses (pests and diseases) and abiotic stresses (drought, salinity, and temperature extremes), sustainable breeding programs can enhance crop resilience and productivity. Drought-tolerant maize varieties developed through the Water Efficient Maize for Africa (WEMA) initiative have reduced yield losses in drought-prone regions (Lim, 2018). Genetically resistant crops reduce reliance on chemical inputs, such as pesticides and fertilizers, which are often associated with ecological harm and increasing pest resistance. Bt cotton, for example, has reduced pesticide use by 37% and increased yields by 24% in India. By integrating biodiversity into breeding programs, these approaches also promote ecosystem stability, reducing the risks associated with monoculture farming systems. Through these efforts, sustainable crop breeding directly addresses food security challenges while contributing to environmental conservation and climate resilience.

1.2 Genetic Resistance Mechanisms

Genetic resistance mechanisms are а cornerstone of sustainable crop breeding. providing plants with the ability to withstand or limit damage caused by pests, pathogens, or environmental stresses. Genetic resistance is defined as the innate capability of a plant to defend itself through specific genetic traits that govern structural, biochemical, or physiological defenses (Zhang et al., 2013). This resistance offers several advantages over traditional pest and disease control methods, such as chemical treatments. Unlike chemical controls, which can lead to environmental degradation and the emergence of resistant pest populations, genetic both cost-effective resistance is and environmentally sustainable. For example, the overuse of fungicides has contributed to the development of fungicide-resistant strains of Phytophthora infestans, the pathogen responsible for potato late blight. Breeding potato varieties with resistance genes such as Rpi-blb1 and Rpi-blb2 has proven effective in controlling this devastating disease without the need for repeated chemical applications. The significance of genetic resistance lies in its ability to address key agricultural challenges while reducing the reliance on external inputs. Resistance mechanisms can be broadly categorized into quantitative qualitative and resistance. Qualitative resistance, controlled by single major genes, provides strong, race-specific protection but is often short-lived due to the rapid evolution

of pathogens. Quantitative resistance, governed by multiple minor genes, is typically more durable and effective against a broader spectrum of pathogens (Parlevliet, 2002). These mechanisms not only protect crops from immediate threats but also contribute to long-term agricultural sustainability by minimizing environmental impacts and ensuring consistent yields.

1.3 Objectives of the Review

The primary objective of this review is to explore the role of genetic resistance mechanisms in advancing sustainable crop breeding programs. By synthesizing recent research on genetic resistance, the review aims to highlight its potential to address the growing challenges of food security and climate resilience. Specifically, the review will provide the molecular and genetic basis of resistance mechanisms, with examples of successful applications in major crops such as maize, rice, wheat, and potatoes. It seeks to evaluate recent advances in breeding strategies. including the integration of molecular tools like marker-assisted selection (MAS) and CRISPR-Cas9 gene editing, which have revolutionized the development of resistant crop varieties. This review will identify critical challenges and opportunities for future research. These include the need to address the trade-offs associated with resistance breeding, such as potential yield penalties, and to develop strategies for overcoming the evolution of pathogen virulence (Walters and Heil, 2007). It will also emphasize the importance of interdisciplinary approaches, genetics, biotechnology, combining and agroecology, to develop resilient and sustainable crop systems. By synthesizing these insights, this review aims to provide actionable recommendations for researchers, policymakers, and agricultural stakeholders working toward a more sustainable future for global food systems.

2. GENETIC RESISTANCE MECHANISMS IN CROPS

2.1 Types of Genetic Resistance Mechanisms

2.1.1 Qualitative Resistance (Major-Gene Resistance)

2.1.1.1 Characteristics and advantages

Qualitative resistance, also known as major-gene resistance, is controlled by one or a few genes that exert a strong effect on a plant's ability to resist specific pathogens or pests (Table 1). These genes, often referred to as resistance (R) genes, typically follow Mendelian inheritance patterns and provide race-specific resistance, meaning they target specific pathogen strains or pest biotypes (Lefebvre and Chèvre, 1995). A hallmark of qualitative resistance is the "genefor-gene" relationship, wherein a plant's R gene interacts with a corresponding avirulence (Avr) gene in the pathogen to trigger a hypersensitive response (HR), resulting in localized cell death that restricts pathogen spread. The primary advantage of qualitative resistance lies in its robustness and rapid action against specific threats. Because major genes often encode proteins nucleotide-binding such as leucine-rich repeat (NLR) receptors, they can guickly recognize pathogen effectors and initiate defense responses. For example, the wheat Lr34 gene provides resistance to multiple rust diseases and is a widely used qualitative resistance gene in global wheat breeding programs. Qualitative resistance genes are relatively easy to transfer into crop varieties using conventional breeding or molecular tools, desirable making them highly for crop improvement.

2.1.1.2 Examples in major crops

In wheat, resistance to stem rust (Puccinia graminis f. sp. tritici), particularly the devastating Ug99 strain, has been achieved using major R genes such as Sr31, Sr24, and Sr50. The durability genes of these varies, as pathogens can evolve new virulence profiles (Didelot et al., 2016). In rice, the Xa21 gene provides qualitative resistance against bacterial blight caused by Xanthomonas orvzae pv. orvzae. In sovbean, the Rps1k gene confers resistance to Phytophthora sojae, a major pathogen causing root and stem rot. These examples illustrate the effectiveness of qualitative resistance in combating specific pests and diseases.

2.2 Quantitative Resistance (Polygenic Resistance)

2.2.1 Characteristics and advantages

Quantitative resistance is governed by multiple minor-effect genes, each contributing incrementally to a plant's defense mechanisms. Unlike qualitative resistance, which is often racespecific, quantitative resistance is typically broadspectrum, offering protection against diverse

pathogen strains and pest species. This form of resistance is more durable because it reduces the selection pressure on pathogens to evolve virulence. thereby delaying resistance breakdown (Van and Gilligan, 2003). The advantages of quantitative resistance include its and ability to provide durability partial resistance under a range of environmental conditions. While the effect of individual genes may be small, their combined action results in significant resistance levels. Quantitative resistance is also associated with less severe trade-offs. as it often involves constitutive defenses or low-cost metabolic adjustments.

2.2.2 Examples in major crops

In rice, quantitative resistance to blast disease caused by Magnaporthe orvzae is controlled by several minor-effect quantitative trait loci (QTLs) such as qBR9-2 and qBR12-1. These QTLs provide durable resistance across multiple ricegrowing regions. In maize, resistance to gray leaf spot caused by Cercosporazeina is associated with QTLs such as *qGLS1* and *qGLS2*, which contribute to polygenic resistance. In potatoes, resistance to late blight (Phytophthora infestans) is often enhanced by stacking QTLs with minor effects, such as those identified on chromosome 9 (Angmo et al., 2023). These examples widespread demonstrate the utilitv of quantitative resistance in modern crop breeding.

2.3 Induced Resistance (Triggered by Biotic/Abiotic Factors)

2.3.1 Role of priming in plant immunity

Induced resistance refers to the enhancement of a plant's defensive capacity after exposure to specific biotic or abiotic stimuli. This phenomenon can be classified into two main types: systemic acquired resistance (SAR) and induced systemic resistance (ISR). SAR is typically triggered by pathogen infection and involves the accumulation of salicylic acid (SA), while ISR is activated by beneficial microbes and is mediated by jasmonic acid (JA) and ethylene (ET) signaling pathways. Priming plays a central role in induced resistance, preparing plants to stronaer and faster defense mount responses upon subsequent attacks. SAR activation involves the expression of pathogenesis-related (PR) proteins, while ISR plant's ability to produce enhances the

secondary metabolites and defense enzymes (Kamle et al., 2020).

2.3.2 Examples of Chemical and Biological Inducers

Chemical inducers such as benzothiadiazole (BTH) mimic salicylic acid and activate SAR, providing resistance to multiple pathogens in crops like wheat and rice. Biological inducers, including plant growth-promoting rhizobacteria (PGPR) such as Pseudomonas fluorescens, trigger ISR in crops like cucumber and tomato, enhancing resistance to root-knot nematodes and bacterial wilt. These methods illustrate the potential of induced resistance as а complementary traditional strategy to breeding.

2.4 Molecular Basis of Genetic Resistance

2.4.1 Role of resistance (R) genes

Resistance (R) genes are central to plant immunity and typically encode receptor proteins that detect pathogen-derived effectors. Most R genes belong to the NLR family, which triggers defense responses upon effector recognition. For example, the Pto gene in tomato recognizes Pseudomonas syringae effectors, activating localized defense mechanisms (Mysore et al., 2002). Advances in genomics have facilitated the cloning and functional characterization of numerous genes. their R accelerating deployment in breeding programs.

2.4.2 Signal transduction pathways (e.g., Salicylic Acid, Jasmonic Acid)

Plant resistance involves complex signaling networks mediated by hormones such as salicylic acid (SA), jasmonic acid (JA), and ethylene (ET). SA signaling is crucial for defense against biotrophic pathogens, while JA and ET pathways are more effective against necrotrophic pathogens and herbivorous insects. Crosstalk between these pathways allows plants to fine-tune their defenses based on specific threats.

2.4.3 Gene editing and functional genomics in resistance identification

The advent of CRISPR-Cas9 has revolutionized the study and engineering of resistance genes. By knocking out susceptibility (S) genes,

researchers have crops created with enhanced resistance. CRISPR-edited rice with a gene mutation the OsSWEET13 in showed resistance to bacterial blight (Oliva et al., 2019). Functional genomics tools such as RNA-Seq and genome-wide association studies (GWAS) have further identified novel resistance loci, paving the way for precision breeding.

2.5 Case Studies of Genetic Resistance in Key Crops

2.5.1 Maize (e.g., Resistance to Fall Armyworm)

Fall armyworm (*Spodoptera frugiperda*) has emerged as a major pest in maize. Breeding efforts have identified resistance QTLs such as *QTLFaw1*, which reduce larval survival and damage in resistant lines.

2.5.2 Soybean (e.g., Resistance to Soybean Cyst Nematode)

Soybean resistance to soybean cyst nematode (*Heteroderaglycines*) is conferred by loci such as *Rhg1* and *Rhg4*. Resistant varieties have significantly reduced nematode populations and yield losses in the U.S. Midwest.

2.5.3 Potato (e.g., Late Blight Resistance)

In potato, the stacking of R genes such as *Rpivnt1* and *Rpi-blb2* has provided durable resistance to late blight. Genetically engineered potatoes with these R genes have shown nearcomplete protection in field trials (Stuthman et al., 2007).

2.6 Strategies for Integrating Genetic Resistance into Crop Breeding Programs

Developing crop varieties with enhanced genetic resistance is essential for sustainable agriculture, and several strategies have been developed to integrate resistance traits into breeding programs (Table 2). These strategies range from traditional approaches selection like mass and backcrossing to advanced genomic tools such as marker-assisted selection (MAS) and genomic selection (GS). Each approach offers unique advantages and faces specific challenges, making it necessary to combine and optimize methods for effective integration of resistance traits.

3. CONVENTIONAL APPROACHES

BREEDING

3.1 Mass Selection and Pedigree Breeding

Mass selection and pedigree breeding are foundational approaches in conventional breeding programs. In mass selection, plants with desirable traits such as resistance to specific pests or diseases are identified and used as parents for the next generation. Pedigree breeding, on the other hand, involves controlled crossing of parents with known genetic backgrounds to create segregating populations, followed by systematic selection over multiple generations (Berry and Linder, 2007). These methods rely heavily on phenotypic evaluations, such as observing disease symptoms or pest damage, under natural or artificial infestation. Mass selection has been widely used in crops like maize and rice to develop locally adapted resistant varieties. Early resistance to rice blast (Magnaporthe oryzae) was developed through mass selection of traditional cultivars that displayed resistance under field conditions in Asia. Pedigree breeding was instrumental in developing rust-resistant wheat varieties by crossing resistant landraces with high-yielding cultivars during the Green Revolution. The simplicity of these methods makes them accessible, especially in resource-limited regions, but they are often time-consuming and less precise compared to molecular approaches.

3.2 Backcross Breeding for Disease Resistance

Backcross breeding is a powerful method for introgressing specific resistance genes from donor parents (often wild relatives) into elite cultivars. The process involves repeated crossing of the progeny with the elite parent to recover the desirable agronomic traits while retaining the resistance gene. This approach has been widely used to transfer major resistance genes (R genes) into crop species. For example, the Xa21 gene for bacterial blight resistance in rice was introgressed from Oryza longistaminata into commercial varieties through backcrossing (Huang et al., 2012). In tomato, the Pto gene for bacterial speck resistance was incorporated into modern cultivars from wild species like Solanum peruvianum. Backcross breeding is effective for transferring single genes but has limitations when dealing with polygenic resistance or quantitative traits. It can result in "linkage drag," where undesirable traits from the donor parent (such as low yield or poor quality) are co-inherited with the resistance gene due to tight genetic linkage (Wall, 2002). This challenge underscores the need for molecular tools to precisely identify and select resistance loci while minimizing linkage drag.

3.3 Challenges in Conventional Methods (e.g., Linkage Drag)

Conventional breeding methods, while effective, face several challenges. One of the most significant is the difficulty of dealing with linkage drag, which occurs when unwanted genetic material from the donor parent is retained along with the desired resistance gene. This is especially problematic in backcross breeding, where resistance genes from wild relatives are often linked to traits such as reduced yield or poor adaptation. For example, earlv attempts to transfer the Sr36 resistance gene for wheat stem rust resulted in reduced grain quality and yield potential in the resulting varieties. Conventional methods are timeconsuming labor-intensive. and often generations of selection requiring several The reliance on phenotypic and testing. screening can also be problematic, as environmental factors can mask the expression resistance traits, leading to inaccurate of selections. These challenges highlight the need for molecular tools like MAS to improve the efficiency and precision of breeding programs.

3.4 Marker-Assisted Selection (MAS)

3.4.1 Advantages of MAS in identifying resistance loci

Marker-assisted selection (MAS) uses molecular markers linked specific to resistance genes or quantitative trait loci (QTLs) to select desirable traits in breeding populations. Unlike conventional methods, MAS allows breeders to screen plants based on their phenotypes, genotypes rather than enabling precise and early selection of resistance traits (Collard and Mackill, 2008). This approach is especially valuable for traits controlled multiple genes those by or with low heritability due to environmental influences.

Resistance Mechanism	Description	Examples/Applications	Advantages	Challenges
Gene-for-Gene Resistance	Involves specific interactions between plant resistance (R) genes and pathogen avirulence (Avr) genes.	Wheat-Puccinia rust system where the R gene detects the Avr gene of the pathogen.	Highly specific, provides strong resistance when R genes are effective.	Pathogen evolution can overcome resistance through Avr gene mutation.
Quantitative Resistance	Resistance controlled by multiple genes, each contributing to overall resistance.	Durable resistance to late blight in potatoes conferred by quantitative trait loci (QTLs).	Broad-spectrum and durable, less likely to be overcome by pathogens.	Complex inheritance, challenging to identify and introgress multiple genes.
Hypersensitive Response (HR)	Localized cell death at the infection site to limit pathogen spread.	Tobacco's HR to tobacco mosaic virus (TMV) through N gene activation.	Effective in preventing pathogen proliferation.	May lead to energy trade- offs and reduced plant growth under heavy pathogen pressure.
Systemic Acquired Resistance (SAR)	Whole-plant resistance activated after localized pathogen attack, mediated by signaling molecules.	Induction of SAR in cucumber by prior infection with Pseudomonas syringae.	Broad-spectrum resistance, effective against a wide range of pathogens.	Requires priming, time lag in activation, and significant metabolic costs.
Induced Resistance (IR)	Triggered by external factors such as biotic or abiotic agents, leading to heightened defensive state.	Application of jasmonic acid to induce resistance against pests in tomato.	Environmentally friendly, compatible with sustainable agriculture.	Variable effectiveness, dependent on environmental conditions and plant genotype.
Horizontal Resistance	Resistance effective against multiple strains of a pathogen, often quantitative in nature.	Resistance to downy mildew in pearl millet derived from landraces.	Durable and less prone to breakdown, suitable for complex pathosystems.	May not provide complete immunity, challenging to achieve high levels of resistance.
Vertical Resistance	Resistance effective against specific pathogen races, typically mediated by single R genes.	Resistance to stem rust in wheat conferred by Sr31 gene.	High level of resistance, effective in race-specific pathosystems.	Short-lived due to pathogen evolution and emergence of virulent races.
RNA Interference (RNAi)	Gene silencing mechanism targeting pathogen genes	Development of papaya resistant to papaya ringspot virus using RNAi	Targeted approach, effective against viruses	Requires advanced technology and may not

Table 1. Genetic resistance mechanisms in crops

Resistance Mechanism	Description	Examples/Applications	Advantages	Challenges
	through RNA molecules.	technology.	and some pests.	be effective against rapidly mutating pathogens.
Epigenetic Resistance	Resistance regulated by heritable changes in gene expression without altering DNA sequence.	Enhanced resistance to fungal pathogens through epigenetic modifications in rice.	Can provide stable resistance, potential for broad-spectrum applications.	Complex regulatory mechanisms, requires further research for practical breeding use.
Structural Barriers	Physical traits such as thick cuticles, trichomes, or lignified cell walls preventing pathogen entry.	Cuticle thickness in barley providing resistance to powdery mildew.	Does not rely on pathogen-specific interactions, reduces pathogen ingress.	Effectiveness varies with pathogen type and environmental conditions.
Antimicrobial Compound Production	Synthesis of secondary metabolites like phytoalexins, phenolics, or alkaloids to inhibit pathogen growth.	Synthesis of phytoalexins in grapevine to resist Plasmopara viticola.	Directly targets pathogen growth, acts as a first line of defense.	High metabolic cost, may reduce yield under non- pathogenic conditions.

(Source: Didelot et al., 2016, Angmo et al., 2023, Mysore et al., 2002)

Table 2. Strategies for Integrating Genetic Resistance into Crop Breeding Programs

Strategy	Description	Examples/Applications	Advantages	Challenges
Conventional Breeding	Selection of resistant varieties through traditional hybridization and backcrossing methods.	Development of rust-resistant wheat varieties, blast-resistant rice varieties.	Cost-effective, utilizes natural resistance, applicable to diverse crops.	Time-consuming, limited by available genetic diversity.
Marker-Assisted Selection (MAS)	Utilization of molecular markers linked to resistance genes for accelerated selection in breeding.	Incorporation of genes like Xa21 for bacterial blight resistance in rice.	Speeds up breeding, increases precision, reduces phenotypic screening costs.	Requires advanced laboratory facilities and expertise.
Genomic Selection (GS)	Prediction of resistance traits using genome-wide markers and computational models.	Improving polygenic resistance traits in maize for disease resilience.	Efficient for traits controlled by multiple genes, reduces breeding cycle time.	High initial investment in genomic data collection and computational resources.

Paul et al.; J. Adv. Biol. Biotechnol., vol. 28, no. 1, pp. 193-211, 2025; Article no.JABB.127939

Strategy	Description	Examples/Applications	Advantages	Challenges
Gene Pyramiding	Combining multiple resistance genes into a single variety to ensure durable resistance.	Development of varieties with combined resistance to rust and powdery mildew in wheat.	Provides broad- spectrum and long- lasting resistance.	Complex breeding processes, may involve linkage drag.
Genetic Engineering	Direct insertion of resistance genes from other species or within the same species.	Bt crops for pest resistance, transgenic rice with Xa genes for bacterial blight resistance.	Enables introduction of novel resistance traits, bypasses sexual compatibility barriers.	Regulatory hurdles, public perception issues, and biosafety concerns.
CRISPR-Cas Technology	Targeted genome editing to introduce or enhance resistance genes in crops.	Development of mildew-resistant tomatoes by editing the Mlo gene.	High precision, potential for quick implementation, no foreign DNA insertion in some applications.	Ethical concerns, off- target effects, need for skilled personnel.
Wild Relatives and Landraces	Exploiting genetic diversity from wild relatives and traditional varieties for resistance traits.	Utilization of wild rice for resistance to sheath blight.	Provides novel resistance genes, enhances genetic base for breeding.	Difficulties in crossability, potential for undesirable traits.
Participatory Breeding	Collaboration with farmers to identify and develop resistant varieties suited to local conditions.	Farmer-selected varieties of beans resistant to pests in sub- Saharan Africa.	Increases adoption rates, ensures locally adapted varieties.	May not align with advanced breeding methodologies, limited scalability.
Biotechnological Tools	Use of omics approaches such as transcriptomics, proteomics, and metabolomics to identify resistance pathways.	Identifying key resistance genes using transcriptomics in potato for late blight resistance.	Provides insights into resistance mechanisms, supports targeted breeding.	High costs, need for interdisciplinary collaboration, complex data analysis.
Integrated Breeding Approaches	Combining multiple methods, such as MAS and GS, for a holistic breeding strategy.	Simultaneous use of MAS and GS for rust resistance in wheat.	Enhances efficiency and accuracy, leverages strengths of multiple strategies.	Requires coordination of different expertise and resources.

(Source: Peshin et al., 2014. McDonald and Linde, 2002, Pilet-Nayel et al., 2017)

The advantages of MAS include:

- **Speed**: MAS can reduce the breeding cycle by allowing selection at the seedling stage, bypassing the need for time-consuming field evaluations.
- Accuracy: By targeting specific markers, MAS minimizes the risk of linkage drag and ensures the efficient transfer of resistance genes.
- **Cost-Effectiveness:** While initial investments in molecular tools are high, MAS reduces the need for laborintensive phenotyping and field trials. long-term resulting in cost savings.

3.4.2 Examples of successful MAS-driven programs

MAS has been successfully used in several crops to develop resistant varieties. In rice, the Xa21 gene for bacterial blight resistance was introgressed into high-yielding varieties using MAS, leading to the release of commercially successful cultivars such as IRBB21. MAS was used to pyramid multiple resistance genes (Pi1, Pi2, and Pi33) for rice blast, resulting in durable resistance across diverse growing environments (Wu et al., 2019). In wheat, MAS facilitated the transfer of rust resistance genes (Yr36 and Lr34) into elite cultivars, enhancing resistance to both stripe and leaf rust. In maize, resistance to the maize streak virus was achieved by identifying and selecting QTLs associated with resistance using molecular markers. These examples demonstrate the transformative potential of MAS in breeding programs, particularly for addressing biotic stresses.

4. GENOMIC SELECTION (GS)

4.1 Concept and Application of GS in Resistance Breeding

Genomic selection (GS) is an advanced breeding approach that uses genome-wide markers to predict the genetic value of breeding candidates. Unlike MAS, which targets specific loci, GS captures the combined effects of all markers across the genome, making it highly effective for polygenic traits such as quantitative resistance (Voss-Fels et al., 2019). This approach relies on the development of a "training population" with known phenotypic and genotypic data, which is used to build predictive models. These models are then applied to untested individuals to predict their resistance potential, accelerating the breeding process. GS has shown promise in resistance breeding by enabling the simultaneous selection of multiple traits. For example, in wheat, GS was used to predict including resistance multiple diseases, to fusarium head blight and rusts, with high accuracy. In potato, GS models were successfully applied to improve resistance to late blight by leveraging genome-wide SNP markers.

4.2 Role of High-Throughput Genotyping and Phenotyping

The success of GS depends on the availability of high-throughput genotyping and phenotyping platforms. Genotyping technologies like genotyping-by-sequencing (GBS) and SNP arrays allow for the rapid and cost-effective generation of genome-wide marker data. Highthroughput phenotyping tools, such as drones imaging systems, enable and precise measurement of disease symptoms and plant traits under field conditions (Chawade et al., 2019). These technologies are critical for building robust training populations and improving the predictive accuracy of GS models. As an example, in maize, high-throughput phenotyping using multispectral imaging was combined with GS to identify resistance to gray leaf spot and northern corn leaf blight, significantly reducing breeding cycle times. These advancements highlight the potential of GS to revolutionize resistance breeding by integrating genomic and phenotypic data at unprecedented scales.

5. GENETIC ENGINEERING AND GENE EDITING

5.1 CRISPR-Cas9 and Its Applications in Resistance Improvement

CRISPR-Cas9, a revolutionary genome-editing tool, has transformed the landscape of crop improvement by enabling precise, targeted modifications to plant genomes. In the context of resistance improvement, CRISPR-Cas9 allows breeders to directly edit genes associated with plant immunity, either by introducing new resistance traits or by knocking out susceptibility (S) genes that pathogens exploit to infect plants. This approach offers unparalleled precision compared to traditional methods, enabling the rapid development of resistant crop varieties with minimal unintended genetic changes. One of the most significant applications of CRISPR-Cas9 has been the modification of S genes. In rice, CRISPR was used to edit the OsSWEET13 and

OsSWEET14 genes, which encode sugar transporters exploited by Xanthomonas oryzae pv. oryzae (the causal agent of bacterial blight). The edited rice plants showed enhanced resistance without compromising yield or other agronomic traits (Mishra et al., 2021). In tomato, CRISPR-Cas9 was used to knock out the SIMIo1 gene, conferring resistance to powdery mildew caused by Oidium neolycopersici. The edited exhibited strong resistance plants while maintaining normal growth and development. CRISPR has also facilitated the introduction of novel resistance traits by enabling precise gene insertions. For example, genes encoding antimicrobial peptides or pathogen effector inhibitors can be inserted into crops to provide broad-spectrum resistance. The simplicity. efficiency, and cost-effectiveness of CRISPR-Cas9 make it a powerful tool for addressing biotic stresses in crops, especially as the technology becomes more accessible and adaptable across diverse species.

5.2 Examples of Engineered Crops with Enhanced Resistance

Genetic engineering has already delivered numerous crops with enhanced resistance to pests and diseases, significantly contributing to global food security. One of the most well-known examples is Bt crops, such as Bt cotton and Bt maize, which are engineered to express insecticidal proteins from Bacillus thuringiensis. Bt cotton, in particular, has dramatically reduced pest damage from bollworms while cutting pesticide use by 37% and increasing yields by 24% in countries like India (Peshin et al., 2014). Another success story is genetically modified papaya, which was engineered to resist the papaya ringspot virus (PRSV) through the insertion of a coat protein gene from the virus. This transgenic papaya, known as the Rainbow variety, saved Hawaii's papaya industry from near collapse in the 1990s. In potatoes, genetic engineering has been used to combat late blight caused by Phytophthora infestans. The insertion of R genes from wild potato relatives, such as Rpi-vnt1 and Rpi-blb2, has produced varieties with durable resistance. Field trials of these transgenic potatoes have demonstrated nearprotection against complete the disease. reducing the need for fungicide applications. The deployment of gene-edited crops is also gaining momentum. CRISPR-edited rice resistant to blast disease (Magnaporthe oryzae) and wheat resistant to powdery mildew have demonstrated the potential of gene editing to address major

biotic challenges in agriculture, 2014. These examples highlight the transformative potential of genetic engineering and gene editing in developing resistant crops, reducing the need for chemical inputs, and enhancing agricultural sustainability.

6. BREEDING FOR DURABILITY OF RESISTANCE

6.1 Concepts of Durability and Epidemiological Considerations

Durable resistance refers to resistance that remains effective over time and across diverse environmental conditions and pathogen populations. This is particularly important in the context of evolving pathogens, which can rapidly overcome single-gene (qualitative) resistance through genetic mutations. To achieve durability, breeders must consider epidemiological factors. such as the genetic diversity of pathogens, their reproductive rates, and their mechanisms of virulence evolution (McDonald and Linde, 2002). A key concept in achieving durable resistance is minimizing the selection pressure on pathogens to evolve virulence. This can be achieved by deploying resistance genes in combination (gene pyramiding) or by using resistance genes with broad-spectrum activity. For example, the Lr34 gene in wheat confers partial, broad-spectrum resistance to multiple rust species and remains effective despite decades of use in breeding programs. Epidemiological considerations, such as understanding the genetic structure of pathogen populations and monitoring for the emergence of virulent strains, are critical for designing strategies that maximize durability.

6.2 Combining Quantitative and Qualitative Resistance for Durability

The combination of qualitative (major-gene) and quantitative (polygenic) resistance offers a promising strategy for enhancing durability. While genes provide strong, race-specific major protection, their effectiveness is often short-lived due to pathogen adaptation. Quantitative resistance, which is governed by multiple minoreffect genes, is generally more durable but provides only partial protection (Pilet-Navel et al., 2017). By combining these two forms of resistance, breeders can develop varieties that achieve both high levels of protection and longterm durability. An example of this approach can be seen in rice breeding, where major genes like Pi2 and Pi54 for blast resistance have been combined with QTLs conferring quantitative resistance, resulting in varieties with durable resistance across different growing environments. In wheat, the combination of *Yr36* (qualitative resistance to stripe rust) with polygenic resistance QTLs has provided effective and lasting protection against rust diseases. This integrative approach leverages the strengths of both resistance types, reducing the risk of resistance breakdown while maintaining high levels of crop productivity.

7. INTEGRATION WITH AGROECOLOGICAL PRACTICES

7.1 Diversified Cropping Systems and Their Impact on Resistance Durability

Diversified cropping systems, such as intercropping, crop rotation, and polycultures, play a crucial role in enhancing the durability of genetic resistance. These practices disrupt the life cycles of pests and pathogens, reduce the build-up of virulent populations, and create ecological barriers to disease spread (Lamichhane et al., 2015) For example, intercropping maize with beans has been shown to reduce the incidence of maize streak virus by lowering the density of insect vectors. Crop rotation, particularly with non-host crops, is another effective strategy for managing soilborne pathogens and nematodes. Rotating soybean with cereals has been shown to reduce soybean cvst nematode populations, complementing genetic resistance provided by Rha1 and Rha4 loci. Βv promoting agroecological diversity, these systems reduce the selection pressure on pathogens to overcome resistance genes, thereby enhancing the durability of resistance.

7.2 Role of Companion Planting and Organic Amendments

Companion planting and organic soil are additional amendments agroecological strategies that can support genetic resistance by creating more resilient cropping systems. Companion planting involves growing different crops together to exploit their complementary traits, such as pest repellence or pathogen suppression. For example, planting marigolds alongside tomatoes has been shown to reduce nematode infestations. enhancing the effectiveness of resistant tomato varieties (Hooks et al., 2010). Organic amendments, such as compost and biochar, can improve soil health

strengthen plant immunity. and These amendments increase soil microbial diversity. promoting the presence of beneficial microbes that induce systemic resistance in plants. Rhizobacteria such as Pseudomonas fluorescens have been shown to trigger induced resistance (ISR) cucumber, systemic in reducing disease severity caused by Pythium ultimum. By integrating these practices with resistance breeding, farmers can create holistic, sustainable systems that reduce the reliance on chemical inputs and enhance the effectiveness and longevity of genetic resistance in crops.

8. CHALLENGES AND LIMITATIONS IN USING GENETIC RESISTANCE IN BREEDING PROGRAMS

The development and deployment of genetic resistance in crop breeding programs have promise immense shown in combating agricultural challenges (Halewood et al., 2018). Various biological, technological, socioeconomic, and regulatory constraints limit the efficiency, durability, and widespread adoption of these approaches. Addressing these challenges is critical for leveraging the full potential of genetic resistance in ensuring food security and agricultural sustainability.

8.1 Evolution of Pathogen Virulence

8.1.1 Breakdown of Resistance genes (e.g., Race-Specific Resistance)

One of the primary challenges in breeding for genetic resistance is the breakdown of resistance genes, particularly those that confer qualitative (race-specific) resistance. These resistance genes often target specific pathogen strains and are effective only as long as the pathogen population does not evolve new virulent races capable of overcoming the gene's defense mechanisms (Anderson et al., 2010). For example, the wheat Sr31 resistance gene, which was effective against stem rust (Puccinia graminis f. sp. tritici) for decades, was overcome by the emergence of the Ug99 strain in East Africa, leading to devastating yield losses in wheat-growing regions. This phenomenon is also observed in rice, where the Xa21 resistance gene provides robust protection against bacterial blight but is ineffective against pathogen strains that have lost the corresponding avirulence gene (avrXa21). The reliance on single resistance genes in monoculture systems creates strong selection pressure on pathogens to evolve virulence, leading to resistance breakdown and

rendering previously resistant varieties susceptible.

8.2 Role of Pathogen Diversity and Adaptability

Pathogens exhibit remarkable genetic diversity adaptability, which complicates the and development of durable resistance. High mutation rates, sexual recombination, and gene flow within pathogen populations enable the rapid emergence of new virulent strains (Arenas et al., 2018). For example, the late blight pathogen (Phytophthora infestans), responsible for potato and tomato infections, has shown exceptional genetic adaptability, frequently overcoming resistance genes like Rpi-vnt1 within a few growing seasons. In maize, the fall armyworm (Spodoptera frugiperda) has evolved resistance to Bt maize in several regions, posing a significant threat to its efficacy. Pathogen diversity also limits the effectiveness of resistance breeding in geographically diverse areas. A resistance gene that works well in one region may fail in another due to differences in pathogen populations. This underscores the need for continuous monitoring of pathogen populations and the deployment of resistance strategies that account for their genetic variability and adaptability.

8.3 Trade-Offs Between Resistance and Other Traits

8.3.1 Yield penalties associated with resistance genes

The incorporation of resistance genes into crop varieties can sometimes result in trade-offs, particularly in the form of yield penalties. Resistance traits often involve metabolic or structural changes that divert resources away from growth and reproduction, leading to reduced yields under non-stress conditions (Blum and Blum, 2011). The wheat Lr34 resistance gene provides durable resistance to leaf rust, but its association with slower grain filling and lower biomass production can lead to yield penalties in high-yielding environments. In rice, the Pi54 resistance gene for blast disease has been linked to reduced seed size and overall grain quality in some genetic backgrounds. These trade-offs create challenges for breeders, as farmers are less likely to adopt resistant varieties if they compromise productivity or profitability. Addressing these yield penalties requires careful genetic background selection and stacking of resistance genes with minimal trade-offs.

8.3.2 Effects on crop quality and marketability

Resistance breeding can also negatively impact crop quality and marketability. For example, some resistance genes are associated with changes in secondary metabolites that affect taste, texture, or nutritional value. In tomatoes, resistance to bacterial wilt has been linked to increased production of phenolic compounds, which can negatively impact flavor (Rodrigues 2022). In and Furlong, potatoes. the introgression of resistance genes from wild relatives has sometimes resulted in undesirable traits, such as increased glycoalkaloid content, which can make tubers bitter and potentially These challenges are particularly toxic. for cash crops and significant export commodities, where consumer preferences and quality standards dictate marketability. Breeding programs must balance the need for resistance with maintaining or enhancing crop quality to ensure farmer and consumer acceptance.

8.4 Technological and Resource Constraints

8.4.1 High costs of advanced genomic tools in breeding programs

The use of advanced genomic tools, such as marker-assisted selection (MAS), aenomic selection (GS), and gene editing technologies like CRISPR-Cas9, has revolutionized resistance breeding (Kumar et al., 2024). The high costs associated with these technologies remain a major limitation, especially for public breeding programs and resource-limited regions. For example, genotyping costs for MAS and GS, require while decreasing, still significant in equipment, reagents, investments and bioinformatics infrastructure. The development and deployment of gene-edited crops involve substantial costs for regulatory compliance, field trials, and intellectual property rights. A study estimated that the average cost of bringing a single genetically modified crop to market can exceed \$136 million. These financial barriers limit the adoption of advanced technologies in breeding programs, particularly in developing countries, where funding for agricultural research is often inadequate.

8.4.2 Lack of infrastructure and expertise in developing regions

Many developing regions, where the need for resistant crops is most urgent, lack the infrastructure and technical expertise required to implement genomic tools in breeding programs. sub-Saharan For example. Africa faces significant gaps in access to high-throughout genotyping facilities, field phenotyping platforms, and skilled personnel (Cudjoe et al., 2023). This limits the ability of local breeding programs to develop and disseminate resistant varieties that address region-specific challenges, such as cassava mosaic virus or maize lethal necrosis. Bridging these gaps requires international collaboration, capacity building, and technology transfer initiatives.

8.5 Socioeconomic and Regulation Challenges

8.5.1 Public perception and acceptance of genetically engineered crops

Public perception of genetically engineered crops remains a significant barrier to the adoption of resistance breeding technologies. Misinformation and skepticism about the safety and environmental impact of genetically modified organisms (GMOs) have fueled resistance among consumers and policymakers, particularly in Europe and parts of Africa. For example, despite the proven benefits of Bt cotton in reducing pesticide use and increasing yields, its adoption has been restricted or delayed in several countries due to public opposition (Raybould and Quemada, 2010). CRISPR-Cas9 and other gene-editing technologies face similar challenges. While these tools do not involve transgenic modifications in many cases, public awareness of their distinction from traditional GMOs remains limited. Overcoming these barriers requires transparent communication about the safety, efficacy, and societal benefits of these technologies.

8.5.2 Regulatory hurdles for approval of Genetically Modified Organisms (GMOs)

The regulatory landscape for GMOs and geneedited crops is complex, inconsistent, and often prohibitive. In many countries, regulatory frameworks for gene-edited crops remain unclear, creating uncertainty for breeders and investors. For example, in the United States, crops edited using CRISPR-Cas9 may avoid certain regulatory hurdles if they do not contain foreign DNA, while in the European Union, such crops are subject to strict GMO regulations (Gupta et al., 2021). These regulatory hurdles significantly increase the time and cost required to develop and commercialize resistant varieties, limiting their accessibility to farmers. The delayed

approval of transgenic brinjal (eggplant) in India, despite its proven efficacy against the fruit and shoot borer, has slowed the adoption of resistance technologies in one of the country's most important crops. Simplifying and harmonizing regulatory processes globally could accelerate the deployment of genetically engineered and gene-edited crops to address pressing agricultural challenges (Zarate et al., 2023).

9. FUTURE IN GENETIC RESISTANCE AND SUSTAINABLE BREEDING

The future of genetic resistance and sustainable breeding lies in the integration of advanced collaborative efforts. technologies, and supportive policies. As the global population grows and agricultural challenges intensify, breeding programs must adopt innovative approaches to enhance crop resilience and productivity. Emerging tools in multi-omics. artificial intelligence, and genomics, combined with international collaborations and robust policy frameworks, offer significant opportunities to address the limitations of current breeding strategies and build sustainable agricultural systems.

9.1 Advances in Multi-Omics Technologies

9.1.1 Integration of genomics, transcriptomics, and metabolomics

Multi-omics technologies, which integrate data from genomics, transcriptomics, metabolomics, and proteomics, represent a transformative approach in plant breeding. Genomics provides insights into the genetic makeup of crops, transcriptomics examines gene expression patterns under different conditions. and metabolomics analyzes the biochemical pathways and compounds involved in plant responses to biotic and abiotic stresses. Together, these technologies provide а comprehensive understanding of the molecular mechanisms underlying resistance traits (Deng et al., 2020). The integration of multi-omics has already yielded significant breakthroughs. In rice, combining genomics and transcriptomics revealed how the Xa23 gene confers resistance to bacterial blight by activating key defenserelated genes. Metabolomic profiling of maize identified secondary metabolites like flavonoids and terpenoids that play critical roles in resistance to fall armyworm (Spodoptera *frugiperda*), providing targets for breeding and genetic engineering. By integrating these datasets, breeders can identify biomarkers associated with resistance traits, accelerating the selection of superior varieties and enabling the development of crops with enhanced resistance.

9.2 Role of Artificial Intelligence and Machine Learning in Data Analysis

The sheer volume of data generated by multiomics technologies requires advanced analytical tools, and artificial intelligence (AI) and machine learning (ML) have emerged as indispensable for managing and interpreting these datasets. AI algorithms can identify patterns and associations across complex datasets, helping to predict how specific genes, metabolites, or environmental factors contribute to resistance traits (Murmu et al., 2024). For example, ML models have been used to predict the genomic regions associated with quantitative resistance to wheat rust by analyzing genome-wide marker data. Al-driven approaches also enhance phenotyping, which is critical for linking genotype to phenotype. Automated phenotyping platforms using drones, robotics, and imaging technologies can assess disease symptoms, plant growth, and stress responses with high accuracy. For example, hyperspectral imaging combined with AI algorithms was used to identify early signs of wheat leaf rust, enabling rapid and precise phenotyping for resistance breeding (Xie et al., 2021). The integration of AI into multi-omics research not only accelerates the pace of discovery but also ensures more precise and reliable predictions for breeding programs.

9.3 Development of Climate-Resilient Crops

9.3.1 Addressing combined stress factors (e.g., Pests and Drought)

Future breeding programs must prioritize the development of climate-resilient crops that can withstand multiple stress factors, including pests, diseases, drought, heat, and salinity. Climate change is exacerbating these stresses, often causing their simultaneous occurrence. For example, drought stress can increase plant susceptibility to pests like aphids, while higher temperatures can accelerate pathogen reproduction rates (Sutherst et al., 2011). Traditional breeding strategies, which often focus on single traits, are insufficient to address these complex interactions. Genomics-based

approaches are enabling the identification of genes that confer resilience to multiple stresses. For example, the DREB family of transcription factors in wheat and rice has been shown to enhance tolerance to both drought and heat, while also activating defense pathways against pathogens. Stacking resistance genes with abiotic stress tolerance QTLs has proven effective in developing varieties that can perform under challenging conditions. Maize well varieties combining resistance to gray leaf spot with drought-tolerance traits have demonstrated superior performance in sub-Saharan Africa.

9.3.2 Examples of recent breakthroughs in climate-resilient breeding

Several recent breakthroughs highlight the potential of advanced breeding for climate resilience. In rice, the development of Sub1 varieties, which carry the Sub1A gene for submergence tolerance, has significantly reduced yield losses in flood-prone areas of South and Southeast Asia. These varieties also incorporate resistance to bacterial blight and addressing multiple blast. challenges simultaneously (Sundin et al., 2016). In wheat, genomic selection has been used to breed varieties resistant to both stripe rust and heat stress, combining markers for resistance genes (Yr18 and Yr36) with QTLs for heat tolerance. Genome editing using CRISPR-Cas9 has been employed to develop tomato varieties with enhanced drought tolerance and resistance to powdery mildew by targeting genes like SIMIo1 and stress-response regulators. These examples demonstrate how innovative breeding strategies can address the complex challenges posed by climate change.

9.4 Collaboration and Capacity Building

9.4.1 Role of international research collaborations (e.g., CGIAR)

International collaborations play a critical role in advancing genetic resistance and sustainable breeding. Organizations like CGIAR (Consultative Group on International Agricultural Research) have been instrumental in developing and disseminating resistant crop varieties globally. For example, CGIAR's International Rice Research Institute (IRRI) has developed high-yielding, disease-resistant rice varieties that are grown across Asia, while the International Maize and Wheat Improvement Center (CIMMYT) has released wheat varieties with durable resistance to rusts in sub-Saharan Africa and South Asia (Ortiz et al., 2008). Collaborative initiatives like the Borlaug Global Rust Initiative (BGRI) have brought together researchers, policymakers, and farmers to combat wheat rust, leading to the release of new varieties like *Ug99*resistant wheat. These partnerships enable the sharing of germplasm, knowledge, and technologies, ensuring that resistance breeding benefits farmers in diverse agroecological contexts.

9.5 Empowering Local Breeding Programs Through Technology Transfer

Empowering local breeding programs is essential developina region-specific for solutions. Technology transfer initiatives, such as those supported by the Bill & Melinda Gates Foundation and the African Orphan Crops Consortium, provide resources and training to breeders in developing countries. For example, the introduction of genomic selection tools to maize breeding programs in sub-Saharan Africa has accelerated the development of stresstolerant varieties adapted to local conditions (Anami et al., 2009). Capacity-building programs, such as CGIAR's Excellence in Breeding Platform, train breeders in the use of modern tools like MAS, GS, and CRISPR, bridging the gap between advanced research and on-theground breeding efforts. These initiatives ensure that the benefits of cutting-edge technologies are accessible to farmers in regions most affected by pests, diseases, and climate change.

9.6 Policy and Funding Support

9.6.1 Need for increased investment in sustainable breeding research

Sustainable breeding programs require investment research substantial in and development to leverage advanced technologies and address emerging challenges. Despite their critical importance, public funding for agricultural research has declined in many regions. For example, in sub-Saharan Africa, agricultural R&D spending as a percentage of agricultural GDP is only 0.5%, far below the recommended 1% target. Increased funding is essential to expand breeding programs, develop climate-resilient varieties, and train the next generation of breeders. Public-private partnerships can also play a crucial role in funding breeding research. The HarvestPlus program, which develops biofortified crops with enhanced resistance and nutritional value, combines funding from governments, NGOs, and private companies to address food security challenges (Paul et al., 2024). Sustained investment in breeding research will be critical to meeting the demands of a growing population and changing climate.

9.6.2 Policies promoting the adoption of resistant crop varieties

Supportive policies are needed to ensure the widespread adoption of resistant crop varieties. Governments can promote adoption by providing subsidies for seeds, offering extension services to educate farmers, and supporting market access for resistant crops. For example. India's National Food Security Mission has promoted the use of rust-resistant wheat varieties, leading to significant yield gains. Streamlined regulatory processes for genetically engineered and geneedited crops are also essential. Simplifying the approval process for CRISPR-edited crops, which are often indistinguishable from conventionally bred varieties, can accelerate their deployment and reduce costs. Harmonizing regulations across countries, particularly in regions like Africa where regulatory frameworks vary widely, will enable faster adoption of resistance technologies (Zwanenberg et al., 2008).

10. CONCLUSION

Genetic resistance is a cornerstone of sustainable crop breeding. offering an environmentally friendly and cost-effective solution to combat pests, diseases, and abiotic stresses. Advances in genomic tools, such as CRISPR-Cas9, multi-omics technologies, and artificial intelligence, have accelerated the identification and integration of resistance traits, enabling the development of climate-resilient crops. Challenges such as pathogen evolution, trade-offs between resistance and yield, and socioeconomic barriers must be addressed. Durable resistance can be achieved bv combining qualitative and quantitative traits, while agroecological practices like diversified cropping systems can enhance its longevity. Global collaboration, capacity building, and targeted investments are essential to empower local breeding programs and ensure equitable access to innovations. Supportive policies and streamlined regulatory frameworks are critical to promote adoption. By integrating advanced technologies with ecological and socio-economic

strategies, genetic resistance can help secure global food systems and agricultural sustainability.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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