

Review

Septoria Leaf Spot of Tomatoes: Historical Insights, Present Challenges, and Future Prospects

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Abstract: Septoria leaf spot (SLS), caused by the hemibiotrophic fungus *Septoria lycopersici*, poses a significant threat to tomato production systems. While fungicides can effectively reduce disease epidemics, planting resistant cultivars remains the most efficient and economical control method. Conventional screening and breeding have identified new sources of resistance to *S. lycopersici* among wild relatives. However, gaps exist in the literature concerning tomato—*S. lycopersici* interactions, such as plant defense mechanisms, fungal pathogenicity mechanisms, and interaction dynamics that can inform the development of durable resistance through additional research. To further enhance host resistance to *S. lycopersici*, molecular methods such as marker-assisted breeding, gene editing, genomic selection, and transgenic approaches can be employed. Moreover, the durability of resistance and efficacy of disease management can be optimized within an integrated pest management (IPM) framework that advances diverse tactics to suppress diseases and improve plant productivity. This review highlights the current understanding of pathogen biology, host genetic solutions, and novel strategies to combat the SLS problem and suggests directions for future research.

Keywords: integrated pest management (IPM); resistance breeding; Septoria leaf spot; *Septoria lycopersici*; *Solanum lycopersicum*



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1. Introduction

The tomato (*Solanum lycopersicum* L.) is the third most extensively cultivated vegetable in the United States [1,2]. Tomatoes, rich in vitamins, minerals, and antioxidants, are experiencing a surge in demand. This is fueled by growing awareness of their nutritional value, the popularity of tomato-based products like ketchup, sauces, and purees in the food processing industry, and their status as a staple ingredient in many cuisines worldwide, from salads and sauces to soups and stews [3]. Similarly, the profitability of the crop in diverse regions appears to drive an increase in production, with global production rising from 177 million metric tons in 2015 to 186 million in 2022 [4]. China, the United States, and India are the top three production regions in the world. In the USA, the gross annual income from tomatoes is around \$11.86 billion [4]. Furthermore, the area under organic tomato production has increased [5].

As in many global areas, conventional and organic tomato production systems in North Carolina and the surrounding regions are constrained by significant challenges from multiple soilborne, foliar, and fruit pathogens [6–9]. One of the crucial challenges tomato growers face, especially in cropping systems that do not rely on synthetic fungicides, is the prevalence of Septoria leaf spot (SLS). This fungal disease threatens tomato crops at various stages of development and can lead to significant yield losses of up to 50%, particularly in regions with favorable environmental conditions [8]. The challenges posed by diseases like SLS highlight the critical need to develop more productive disease management strategies.

Moreover, climate changes can affect pathogen growth and increase disease outbreaks [10]. Although synthetic fungicides are effective in conventional tomato production, their use is not feasible in organic farming. To minimize losses, the best approach is integrating disease management tactics such as crop management practices, field sanitation, approved organic or conventional fungicides, biological control approaches, and planting-resistant cultivars.

Advances in understanding SLS have illuminated various aspects of the pathogen's biology, plant–pathogen interactions, and potential resistance mechanisms. Despite these advances, significant research gaps persist. The precise molecular mechanisms underlying tomato resistance to *S. lycopersici* are poorly understood [11]. There is a need to identify and characterize additional resistance genes and to understand how multiple minor quantitative trait loci (QTLs) collectively contribute to resistance. Moreover, the lack of high-quality whole genome information for *S. lycopersici* represents a significant barrier to fully comprehending host–pathogen interactions. Obtaining and analyzing such genomic data are crucial for identifying functional effectors associated with pathogenesis and for developing DNA-based detection tools.

The genetic makeup of tomatoes has been publicly available through genome sequencing (<https://solgenomics.net/>, accessed on 12 August 2024), which provides an opportunity to identify new resistance genes and find molecular markers that are closely linked to these genes. Furthermore, the development of advanced genomic tools and breeding approaches, such as marker-assisted selection (MAS), gene editing (GE), and genomic selection (GS), is essential for effectively incorporating these resistance traits into commercial cultivars. Moreover, the durability of resistance and efficacy of disease management can be optimized within an integrated pest management (IPM) framework that advances diverse tactics to suppress diseases and improve plant productivity. Addressing these research gaps will enhance the ability to develop tomato varieties with robust and lasting resistance to SLS, a vital component of supporting sustainable and productive tomato cultivation. Finally, the depth of the literature and scientific innovations on *S. lycopersici* and SLS is relatively shallow compared to other diseases of tomatoes. This review combines historical and recent work to provide a framework that can enhance the capacity for future work.

2. The Genus *Septoria* and Morphology of *S. lycopersici*

The genus *Septoria*, classified as ascomycete pycnidia-producing fungi, is one of the largest genera of plant pathogens. Numerous species of *Septoria* have a *Mycosphaerella*-like sexual stage (e.g., *Septoria tritici*); however, most have an unknown sexual stage [12–14]. *Septoria* spp. cause leaf and fruit spot diseases in diverse crops such as field crops, forages, and tomatoes. The genus has a wide range of hosts, with an estimated 1072 species and over 3000 taxa [14,15]. Taxonomists commonly accept a broad definition for *Septoria* spp., encompassing fungi that develop pycnidial conidiomata characterized by holoblastic, hyaline, smooth-walled conidiogenous cells with sympodial and percurrent proliferation, along with hyaline, smooth, filiform to cylindrical multi-septate conidia [14]. Host specificity served as the primary criterion for distinguishing *Septoria* species for an extended period due to limited data on morphological characteristics and substantial variability. Thus, *Septoria* species exhibiting similar morphology but differing hosts were classified as distinct taxa [14]. Nonetheless, Beach (1918) demonstrated that relying solely on host specificity for identifying *Septoria* spp. is unreliable, as numerous species within *Septoria* are not limited to a single host but exhibit broader host ranges [16]. For example, *S. lycopersici* can infect multiple plant species within a genus and among closely allied relatives (see below Section 3).

Among the various *Septoria* species, *Septoria lycopersici* is a key tomato pathogen that causes leaf spots known as Septoria leaf spot (SLS). It has the potential to significantly impact cultivated tomatoes in many countries, including the USA [11,17]. Despite its widespread occurrence, it has received limited research attention. The pathogen can cause complete defoliation of tomato plants, resulting in significant crop loss of up to 50%, as documented in the northeastern regions of the USA and Canada [8,18,19]. It is also a severe problem in North Carolina and surrounding states.

This fungus has only a known asexual stage, so it mainly reproduces by forming conidia in pycnidia, which are discharged and dispersed through rain or irrigation splash [20]. The phylogenetic relationships of 104 isolates of *S. lycopersici* were analyzed based on multi-locus sequencing analysis of calmodulin (*Cal*), β -tubulin (*Tub*), and elongation factor 1- α (*EF1- α*). The results showed that the strains from diverse geographic regions are highly clonal, apparently belonging to a single clonal lineage [21].

For *S. lycopersici*, two types of mycelia have been reported: one hyaline with thin walls, typically associated with young, newly emerging mycelium from the germinating conidia and a second type observed as brown-walled cells related to older, well-grown mycelium, which is also responsible for forming pycnidia [22]. These brown, thick-walled mycelium aggregate and integrate into the leaf tissues to form the pycnidial cavity beneath the epithelial layer of host tissue and mainly beneath the stomata. This fungus usually forms pycnidia within two weeks after inoculation. Pycnidia are dispersed to confluent, amphigenous, predominantly epiphyllous, initially immersed, later slightly emergent, and unilocular, measuring 95–160 μm in diameter [22,23]. Conidiophores extend from the pycnidial wall and bear conidia (pycnidiospores). Conidia are holoblastic, filiform, slightly curved to sigmoid, with thin walls, subtruncate at the base, subacute to acute at the apex, attenuated somewhat towards the apical portion, guttulate, subhyaline, measuring $40\text{--}160 \times 2\text{--}3 \mu\text{m}$, and possessing 5–10 distinct septa [23]. Conidia are formed in a basipetal fashion inside the pycnidial chamber and fill the entire chamber, leading to an internal force on ostioles and subsequent conidia release. Ostioles are usually formed by generating pressure on the pycnidial wall, usually by the tension between the epidermal cells, enlargement of the pycnidium, and the pressure exerted by the conidia mass on the pycnidial wall. The ostioles are circular to subcircular, reaching up to 60 μm in width. The conidia germinate after 24–48 h of inoculation under favorable temperature and moisture conditions. The germinating conidia usually swell due to imbibition of water. The germ tube formation can be seen from the inner and apical cells (Figure 1) [22]. The mycelia are intercellular and enter the host cells using globular haustoria for nutrition [22,24].

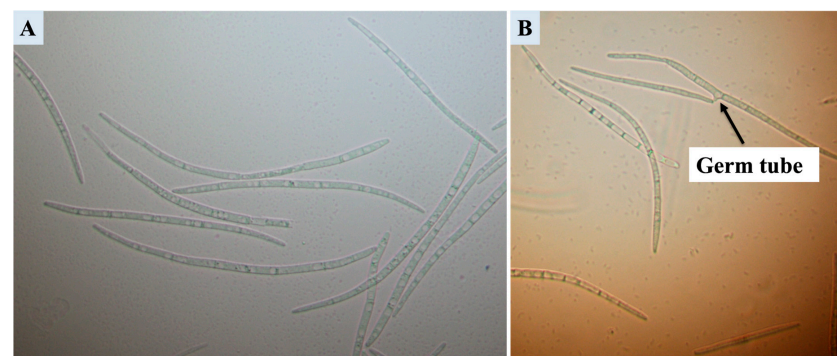


Figure 1. *Septoria lycopersici* spore size and germination. (A) Conidia at $40\times$ magnification observed under a Nikon eclipse 80i (Nikon Instruments Inc., Melville, NY, USA) upright fluorescence phase contrast microscope. (B) Germinating conidia with bulbous germ tube formation at $40\times$ magnification after 2 days of incubation.

3. Host Range and Disease Distribution

Septoria lycopersici is prevalent worldwide, and it was first identified in Argentina in 1982 [25]. In the USA, it was first reported in 1895 in New Jersey [26]. The disease is most severe in areas with prolonged wet and humid weather conditions in the world [27]. However, for unknown reasons, SLS has not been reported from North Asia (Russia and nearby countries). *S. lycopersici* can infect several alternate hosts such as *Capsicum annuum* (bell pepper), *Cyphomandra* spp. (tree tomato), *Lycopersicon* spp. (wild tomatoes), *Datura stramonium* (Jimsonweed), *Petunia* spp. (Petunia), *Physalis* spp. (Gooseberry), *Solanum carolinense* (horsenettle), *Solanum floridanum* (Florida Maple), *Solanum mammosum* (Nipplefruit), *Solanum melongena* (eggplant), *Solanum tuberosum* (potato), *Solanum nigrum*

(black nightshade), *Solanum viarum* (tropical soda apple), *Solanum paludosum* (creeping daisy), *Solanum sessiliflorum* (Longleaf wood oats), *Datura metel* (Devil's trumpet), and *Solanum athiopicum* (African eggplant) [21,28].

4. Disease Symptoms

Septoria lycopersici is a hemibiotrophic fungus with biotrophic and necrotrophic phases during infection [29]. It can infect all aerial parts of the tomato plant, with rare fruit infections [30]. Symptoms usually appear on older, lower leaves and stems at first fruit set in the field. In Zambia, *Septoria* isolates could be divided into type 1 (T1) and type 2 (T2) groups based on the symptoms displayed on infected leaves [27]. T1 isolates produce standard dark brown patches measuring 5 mm in diameter, whereas T2 isolates produce grayish-brown lesions with several concentric rings ranging from 4 to 12 mm in diameter, which are unusual. However, in most tomato-producing regions worldwide, symptoms are consistent with those formed by T1 isolates [31].

In the field, symptoms caused by *S. lycopersici* first appear as small, round, or oval lesions on lower leaves and gradually develop into necrotic lesions with a tan or light gray center [18,20,32–35]. The petioles, stem, and calyx can also exhibit similar symptoms. Necrotic patches on older leaves could have a yellow halo surrounding the lesion and frequently merge, giving a blighted appearance (Figure 2). One of its characteristics is the presence of pycnidia, the fungal fruiting bodies, in the tan centers of the spots (Figure 2) [36]. The pycnidial wall erupts, releasing the conidia [37]. Spotted leaves eventually turn yellow and die prematurely, causing premature defoliation. This defoliation typically starts with the oldest leaves and can quickly progress up the plant toward new growth. Early defoliation can result in significant yield losses [30].

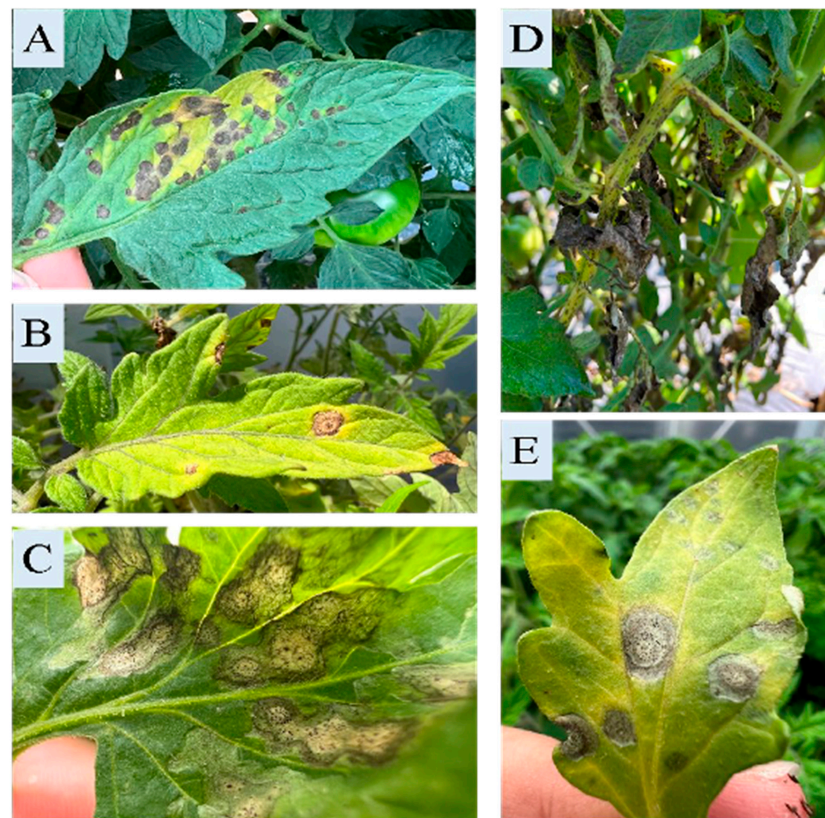


Figure 2. Symptoms of *Septoria* leaf spot infection on tomato plant collected from the greenhouse, Mills River, North Carolina (A) Dark brown necrotic patches on tomato leaves similar to the symptoms formed by T1 isolates [31]. (B) Grayish-brown lesions with several concentric rings similar to symptoms formed by T2 isolates of *Septoria lycopersici*. (C,E) Small dark dots are pycnidia formed on the surface of the infected leaf area. (D) Symptoms seen on leaflets and stems after severe infection.

5. Disease Epidemiology

The fungus can persist on crop or solanaceous weeds (such as horsenettle, nightshade, jimsonweed, and other solanaceous plants), host debris in the soil, and infected seeds as resting structures such as mycelium and conidia within pycnidia [38–41]. This fungus forms conidia in pycnidia under moist conditions; these conidia need at least 24–48 h of 100% relative humidity to germinate and cause infection [24,36]. They can be spread to healthy tomato leaves by various means, including splash dispersal from irrigation or rain events, wind-borne water droplets, and insects. The conidia infect the tomato plant usually through stomata [41–43], with less evidence of direct penetration [4,40]. After infecting a host, initial symptoms typically appear within six days. Pycnidia generally form within two weeks on brown to black leaf spots; conidia are released from these pycnidia as cirrus, a ribbon-like mass of mucus-bound conidia (Figures 2–4) [18,41]. The release of conidia leads to secondary infection cycles (Figure 3). The optimum temperature range for infection, symptom development, and pycnidia formation is 20–24 °C, with a minimum and maximum growth temperature ranging from 5 °C to 27 °C. Studies have shown that conidia become non-viable, resulting in fewer spots when exposed to temperatures higher than 30 °C for an extended period [36,41]. Conidia within pycnidia can survive on infected tissue for up to three years [39,44]. The SLS epidemics are favored by high rainfall, high humidity, and moderate temperatures [26].

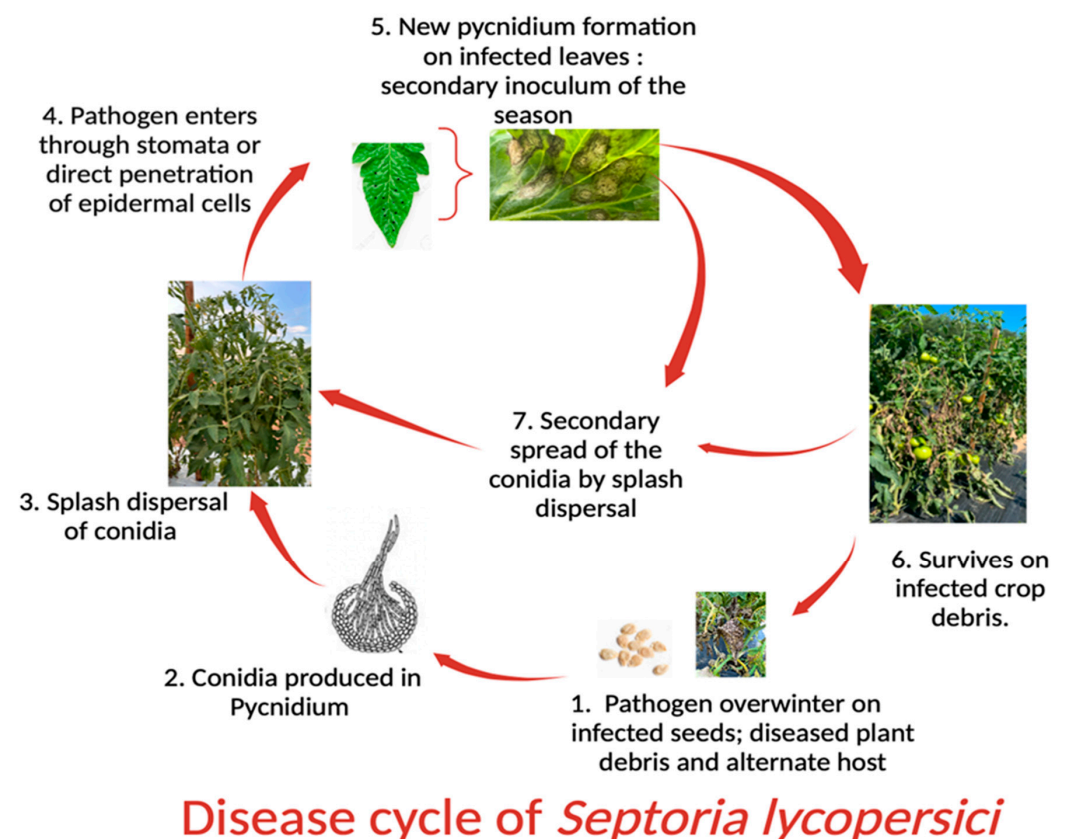


Figure 3. Proposed disease cycle of *Septoria lycopersici* in the tomato [45]. However, all photos of disease symptoms were initially obtained from our *Septoria* research plots in Mills River, North Carolina.

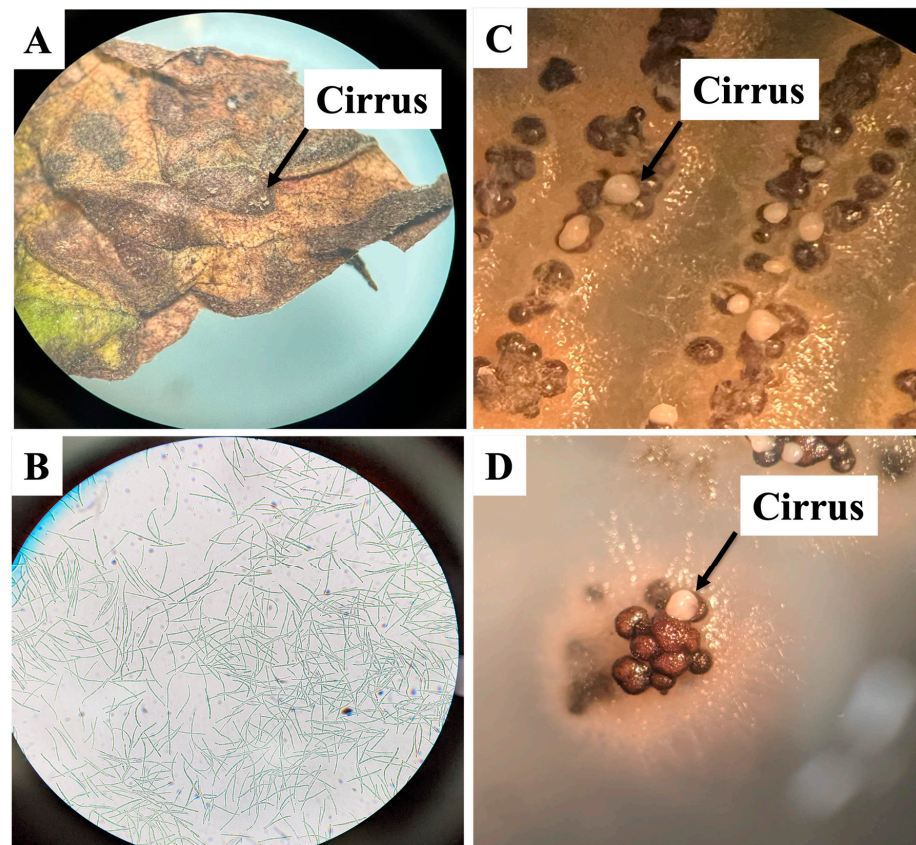


Figure 4. Pycnidia, cirrus, and conidia formed at the surface of tomato leaves and potato dextrose agar (PDA) medium. (A) Cirrus was visualized under a Steriobinocular microscope at the surface of infected tomato leaves. (B) Conidia observed under 20× magnification. (C) Cirrus was seen on the surface of PDA plates inoculated with *Septoria lycopersici* with unaided eyes. (D) Cirrus was observed on media under a microscope.

6. Detecting and Identifying *Septoria* Using Current and Emerging Techniques

There is a pressing need for new detection tools and identification methods for *S. lycopersici*, as there is a gap in current diagnostic techniques. Traditionally, the pathogen has been identified using morphological and microbiological methods, focusing on the signs and symptoms that develop on the aerial parts of the host, the characteristics of hyphal cells, and the presence of distinct pycnidia and conidia morphology. The pathogen can be identified by observing the size of the hyphal cells, which average $15.90 \times 3.10 \mu\text{m}$ and have infrequent branching in mycelium [46]. The pycnidia are noted for their hollow, globose bodies lacking a distinct ostiole. *S. lycopersici* displays optimal mycelial growth on potato dextrose agar (PDA). In contrast, clarified V8 juice agar, ¼ strength PDA, and oat-meal agar (OMA) enhance sporulation with filiform conidia varying in septation (0–9 septa) and featuring blunt or pointed ends.

The available studies do not record molecular diagnostic tools, representing a gap in current diagnostic methods that could aid future diagnosis, detection, and identification protocols. Efficient detection, especially of seed-borne inoculum, and accurate fungus identification are crucial for effective disease management. Methods have been developed for closely related fungi. For example, a fluorescent real-time PCR assay has been designed to measure the fungal biomass of *Mycosphaerella graminicola* (anamorph: *Septoria tritici*) in wheat [47]. Specific primers were created from β -tubulin gene sequences that amplified a PCR product of 100 bp from pure cultures of the fungus and infected wheat leaves. The real-time PCR assay was also helpful in assessing biomass to distinguish between resistant and susceptible wheat cultivars. Likewise, the qPCR assay was a powerful diagnostic tool for *Mycosphaerella* leaf spot diseases of bananas, with applications in

surveillance, disease forecasting, and disease resistance testing [48]. Alternatively, established and emergent detection technologies to explore include serological fungal detection assays, loop-mediated isothermal amplification (LAMP), clustered regularly interspaced short palindromic repeats (CRISPR)-based detection, nucleic acid-based biosensors, and paper-based microfluidic devices [49–52]. Most of these techniques require unique genomic sequences of the pathogen for rapid and accurate identification, a current gap with *S. lycopersici*. We have sequenced three field isolates of *S. lycopersici* from North Carolina and are currently analyzing the data. This sequencing project aims to identify functional effectors involved in *S. lycopersici* pathogenesis and explore simple sequence repeats (SSRs) to assess genetic differentiation among U.S.A. populations. The resulting whole-genome sequencing data should aid in developing DNA-based detection tools and advance research on pathogen biology, plant-pathogen interactions, and integrated disease management strategies.

Another emerging area of productive research will incorporate remote sensing and imaging combined with machine learning and artificial intelligence technologies. This will enhance disease diagnosis, particularly at early stages, enabling better disease management in tomato populations and helping to phenotype plants in breeding programs [53,54].

7. Pathogenesis

Understanding the pathogenesis of *S. lycopersici* is essential for devising effective strategies for disease prevention, diagnosis, treatment, and developing host resistance. However, there is still limited research on the pathogenesis mechanisms of *S. lycopersici* in tomatoes. An α -tomatine (steroidal glycoalkaloid) belonging to the saponin family has been shown to confer antifungal activity in SLS-resistant tomato cultivars. However, *S. lycopersici* produces an extracellular tomatinase enzyme to hydrolyze the α -tomatine and cause infection [43,55,56]. To understand the role of the tomatinase enzyme, Martin-Hernandez et al. [43] conducted an experiment using a mutated strain of *S. lycopersici* lacking the tomatinase gene. They found that the tomatinase gene plays some role in disease development but is not the sole factor. Additional research is needed to elucidate further the precise mechanisms underlying the role of tomatinase.

Additionally, research indicates that the jasmonic acid-mediated defense pathway may not significantly resist *S. lycopersici* in tomatoes [29]. However, the ethylene signaling pathway might be involved, though the exact mechanism requires further investigation [57]. Several elicitor molecules have been shown to induce resistance to different pathogens, but the specific mechanisms of host resistance suppression against *S. lycopersici* remain poorly understood [58,59].

To advance tomato breeding for resistance against *S. lycopersici*, it is crucial to identify the genes that confer resistance. In instances where a single dominant gene confers resistance, such as *Stb19* in wheat against *Zymoseptoria tritici* [60], the plant's resistance genes (*R*) recognize specific avirulence (*Avr*) genes of the pathogen, leading to resistance activation [61]. In many pathosystems, localized plant defenses are swiftly activated at infection sites, limiting pathogen invasion [62]. Pattern-recognition receptors (PRRs) on the cell membrane detect pathogen-associated molecular patterns (PAMPs), triggering PAMP-triggered immunity (PTI) [63,64]. In compatible interactions without *R* proteins, pathogens evade PTI within host tissues by altering or suppressing their elicitor expression, subverting effector-triggered immunity (ETI), and causing effector-triggered susceptibility (ETS) [65–67].

Advanced genomic tools and modern breeding approaches, such as marker-assisted selection, gene editing, and genomic selection, are pivotal to advancing tomato resistance to *S. lycopersici*. Thus, a detailed understanding of the molecular intricacies of tomato—*S. lycopersici* interactions combined with emergent methods is indispensable for developing effective and lasting resistance strategies. This knowledge will inform the creation of robust tomato cultivars capable of withstanding *S. lycopersici* infections, contributing to the goal of more sustainable and productive tomato cultivation.

8. Current Disease Management Strategies for SLS

Effective disease management strategies are available for many tomato diseases. However, SLS is particularly complex, and with the impact of climate change, designing effective management programs may become even more challenging. Furthermore, the literature and well-developed IPM practices are limited to managing SLS. Therefore, developing new disease management tools for SLS that can complement existing tactics is crucial. These tools should be sustainable, economical, and efficient to ensure that tomato growers can implement the best solutions for their needs.

8.1. Cultural Methods

Proper sanitation methods can reduce inoculum loads in the field and reduce the spread of pathogen infections in crops. One of the most effective ways to achieve this is by removing or burying plant debris after harvest [17,68]. Many growers may leave living tomato plants in the field due to busy schedules; this enables the pathogen to multiply inoculum loads in the field and increases the risk of epidemics in subsequent tomato crops. Since the pathogen dwells on host debris, crop rotation to a non-susceptible host is also an important tactic to encourage tomato debris desiccation [18].

Disease-free seeds can significantly reduce the risk of introducing the pathogen into new crops [69]. Appropriate seed treatment techniques and routine monitoring should be implemented to optimize the health and productivity of the plants. Sanitation also involves removing volunteer seedlings in the field, alternative weed hosts near the field, and removal of any tomato seedling transplants showing disease symptoms before planting them in the field. As with other “splash-dispersed” pathogens, avoiding contact with plants when wet can reduce inoculum spread [17]. Following these practices can reduce the risk of disease and an epidemic that threatens yield loss.

8.2. Chemical Fungicides

Disease control can be achieved through repeated applications of fungicides [34,70]. Efficacy experiments demonstrate pydiflumetofen, difenoconazole, benzovindiflupyr, chlorothalonil, azoxystrobin, and metconazole were the most effective fungicides in controlling *Septoria* in tomatoes [71–73]. Another study showed that combining cover crop mulch of winter rye and hairy vetch with weekly fungicide application led to significantly lower area under disease progress curve (AUDPC) values for SLS and higher marketable yields [74]. However, it is essential to note that reliance on fungicides can lead to the emergence of fungal pathogens that evolve resistance to one or more modes of action, which is a significant challenge for the future efficacy of fungicides. To address this, future research should explore new techniques, such as qPCR, to detect resistance mutations in *S. lycopersici* populations. Furthermore, it is essential to implement fungicide resistance management measures to reduce the risk of emergent fungal-resistant populations [75]. Integrating non-chemical disease management tools or pest management (IPM) strategies with fungicides can enhance product stewardship and profitability.

8.3. Botanical Pesticides and Inducers of Host Resistances

Due to the limited availability of commercial cultivars with host resistance, researchers are exploring alternative methods to induce systemic acquired resistance (SAR) in tomatoes. Synthetic and natural products and peptides have been investigated to manage SLS. For instance, κ -carrageenan, a substance found in marine red seaweed (*Kappaphycus alvarezii*), elicited SAR in susceptible tomato cultivars and enhanced their tolerance to *S. lycopersici* infection [76]. Moreover, eight botanicals (fresh leaves of *Pongamia pinnata*, *Bougainvillea glabra*, and *Eucalyptus globule*, as well as *Tagetes erecta*, and fresh *Allium sativum* bulbs) based on indigenous technical knowledge (ITKs) were used to control *S. lycopersici*. Among these, *Allium sativum* (65.10%) extract was found to be the most effective in preventing the growth of *S. lycopersici* [77]. To date, such compounds are not routinely available for commercial growers.

8.4. Biological Control

Some growers prefer biological control agents (BCAs) because they have high toxicological safety and a lower environmental impact. BCAs have been used to manage plant diseases in conventional and organic tomato production systems. For instance, treating seeds and seedlings with *Bacillus subtilis* can significantly reduce several tomato foliar diseases, such as early blight, SLS, and powdery mildew [78]. Mycelial growth filtrate and mycelial extract of *Ganoderma lucidum* can reduce disease severity and fungal spore germination by 90% and 60% on tomato plants, respectively. It can also induce tomato resistance against *S. lycopersici* [79]. Similarly, *Fusarium solani* strain Fs-K is an endophyte that can reduce the impact of soil and foliar pathogens [57]. Interestingly, this endophyte can induce systemic resistance (ISR) in tomatoes against *S. lycopersici* [57]. *Trichoderma harzianum*, another prominent BCA, is also effective in managing *S. lycopersici* [80]. It is not clear how widespread the use of these BCAs is in commercial tomato production systems. Still, as the science and practice of these methods improve, microbiome-based biological solutions against *S. lycopersici* could be a practical approach to managing tomato diseases in the future. Integrating sanitation, cultural, biological, and chemical techniques can help mitigate SLS epidemics [17,81,82].

8.5. Novel Sources of Disease Resistance

Wild tomato species are significant sources of resistance to *Septoria lycopersici*. Some tomato species like *Solanum pimpinellifolium*, *S. chilense*, *S. habrochaites*, *S. peruvianum*, and *S. cerasiforme* have been reported to be resistant to SLS, with *S. hirsutum*, *S. habrochaites*, and *S. peruvianum* as the best sources of resistance (Table 1) [19]. Domesticated tomatoes (*S. lycopersicum*) are the most susceptible *Solanum* accessions tested [34]. To date, resistance to SLS has been identified as a non-race-specific or quantitative trait loci (QTL). The resistance was first found in *L. hirsutum* (PI 126445) and incorporated into *L. esculentum* (Rutgers) to produce SLS-resistant tomatoes [19]. Similar efforts were made to transfer SLS resistance from *L. peruvianum* to *L. esculentum* [25,83]. These findings were based on phenotypic evaluation rather than genomic information, as only phenotypic assessment was conducted to confirm the incorporation of resistance in the progenies.

Table 1. List of novel sources of resistance to *Septoria lycopersici* in tomatoes.

<i>Solanum/Lycopersicon</i> Species	Host Response	Accession	Reference
<i>S. peruvianum</i> (Syn: <i>Lycopersicon peruvianum</i>)	Highly resistant	LA-1910, CNPH-1036, LA-1984, PI 306811, LA1677, LA2744, LA 1113-1	[34]
		LA1675, LA1360, PI251307, PE-33, PI 270435, PI 390655	[84]
		PI 126944	[83]
		PI127829	[33]
	Resistant	LA-0107, LA-1113-2, LA-1270, CGO-6711, LS-121, CGO-6708, CGO-6716, LA-2067, CGO-6709, CNPH-1033, ID-8624, CGO-8200, PI-128660, PI-365951, LA-1626	[34]
		PI 126431, PI 128656, PI 127832	[19]
	Moderately resistant	LA-1292, LA1304, PI 365951, PI 128654, PI 390671, PE-32, LA1723, LA1983, PE-48, PE-31, PE-22, PI 415127	[84]
	Segregating	PI 126926, PI 126928, PI 126930, PI 126944, PI 126945, PI 126946,	[19]
	Segregating	PI 128645, PI 128652, PI 128653, PI 128655	[19]
<i>S. hirsutum</i> (Syn: <i>L. hirsutum</i>)	Highly resistant	LA-2100, LA-2650, LA-2204, PE-36	[84]
		PI 126445	[34]
	Resistant	LA-1366, LA-2124, LA-255	[84]
		PI 126446, PI 126447, PI 127826, PI 126936	[19]
	Moderately resistant	PI 365934, PE-34, PI 390513, PI 251305	[84]

Table 1. Cont.

<i>Solanum/Lycopersicon</i> Species	Host Response	Accession	Reference
<i>S. habrochaites</i>	Highly resistant	CNPH-1112	[34]
	Resistant	WIR-3611, PI 126445, PI 134417, PI 127826, PI 134418, PI 127827, WYR-7924, L-03683	[34]
<i>S. pimpinellifolium</i> (Syn: <i>L. pimpinellifolium</i>)	Highly resistant	PI 422397	[70]
		LA 0722	[33]
	Resistant	PI 126925, LA 1342, CNPH-0769	[34]
	Moderately resistant	PI 422397, LYCA/66, PE-8, PE-12, PE-3, PE-14	[84]
<i>S. lycopersicum</i> (Syn: <i>L. esculentum</i>)	Highly resistant	LA1800	[83]
	Resistant	Hawaii 7996, Santa Cruz	[34]
	Moderately resistant	PI 111406, PI 372364, PI 427149, PI 438875, PI 97321, PI 262892, PI 270418, PI 312188, PI 452027	[84]
<i>S. lycopersicum</i> var <i>cerasiforme</i> (Syn: <i>L. esculentum</i> var. <i>cerasiforme</i>)	Moderately resistant	PE 64, PE 69, PE 78	[84]
<i>S. chilense</i> (Syn: <i>L. chilense</i>)	Highly resistant	LA 460	[33]
	Resistant	LA 1967	[34]
	Moderately resistant	LA 1960, LA 2404	[84]
<i>S. lycopersicum</i> × <i>S. peruvianum</i>	Highly resistant	TX-407, CNPH-0979	[34]
	Resistant	TX-410, TX-412, CNPH 0980	[34]
<i>S. cerasiforme</i>	Resistant	CNPH-0633	[34]
<i>S. corneliomulleri</i> J. F. Macbr.	Resistant	PI 126448	[85]

Breeding tomatoes for disease resistance has been a major focus [86], yet publicly available information on the chromosomal location and markers for selecting lines with SLS resistance remains limited. Over 700 tomato accessions were evaluated for SLS resistance, with only a few moderately resistant lines found among tomato wild relatives [84]. Among 124 wild and domesticated *Solanum* spp. accessions, 10 were highly resistant, and 33 were moderately resistant to SLS in greenhouse and field screenings [34]. Additionally, *Lycopersicon pimpinellifolium* (Jusl.) Mill has been identified as having moderate resistance to SLS, controlled by a single dominant gene [70,83]. However, this specific tomato line has not been incorporated into tomato breeding programs due to its moderate resistance level and its association with small fruit size and late ripening. A research team from West Virginia University (WVU) in the United States is developing a tomato line with strong resistance to SLS. To do this, they are using in vitro ovule culture, an advanced plant breeding technique, to cross-cultivate tomato varieties with wild species known for their robust SLS resistance. The team identified two wild tomato species, *S. peruvianum*, and *S. arcanum*, as sources of strong SLS resistance. By employing in vitro ovule culture, they overcame barriers that typically hinder successful hybridization between cultivated and wild tomato species, resulting in the production of the BC3 generation. The main objective of their research is to create a new tomato line that retains the desirable traits of cultivated tomatoes, such as high yield and good fruit quality, while incorporating the strong disease resistance found in wild species. If successful, this new tomato line could provide a sustainable solution for managing SLS, reduce dependence on chemical fungicides, and improve crop resilience. In addition, the researchers are investigating the genetic basis of SLS resistance. They have identified that the resistance is likely oligogenic, with three loci on chromosomes 2, 8, and 11 potentially involved in conferring resistance to the disease [87,88]. Despite the identification of resistance in various wild relatives and breeding lines, no commercial tomato cultivars are available that offer satisfactory SLS resistance for growers.

9. Potential Genomic Tools and Modern Breeding Approaches: Implications for *S. lycopersici*

Innovative genomics technologies, such as next-generation sequencing (NGS), high-throughput marker genotyping, and omics technologies, have emerged as powerful tools for understanding genome variation in tomatoes at the DNA, RNA, and protein levels. New genetic approaches, such as advanced-backcross quantitative trait loci (AB-QTL) analysis, genome-wide association studies (GWAS), and genomic selection, can harness genetic variation in cultivated tomatoes and wild relatives.

From conventional breeding practices to marker-assisted selection (MAS). Breeding for SLS resistance in an elite line of tomatoes can be challenging for a few reasons. Successful disease phenotyping requires consistency and reliability. However, scoring quantitative phenotypes, such as disease resistance, often leads to high variance in data. In recent decades, phenotyping has not advanced as much as genotyping developments in molecular biology [89]. Phenotyping for SLS resistance is subjective. Transformation of scales has been developed to mitigate this problem [90]. Additionally, phenotyping requires significant labor time; this may be mitigated through emerging digital methodologies [91].

Another challenge is the lack of genetic variation in cultivated tomato lines when using MAS [92]. Domesticated tomatoes only possess 5% of the genetic diversity found in their wild counterparts [93]. Despite these limitations, conventional breeding by MAS (Figure 5) has been used since the 1980s and can significantly speed up traditional breeding efforts while lowering the expense and associated work [94]. MAS work is limited for SLS; two RAPD markers were associated with SLS susceptibility, whereas three RAPD markers were linked to SLS resistance alleles [95]. Due to the absence of a significant gene or QTL associated with SLS resistance in tomatoes, molecular breeding for SLS has not been contemplated [11].

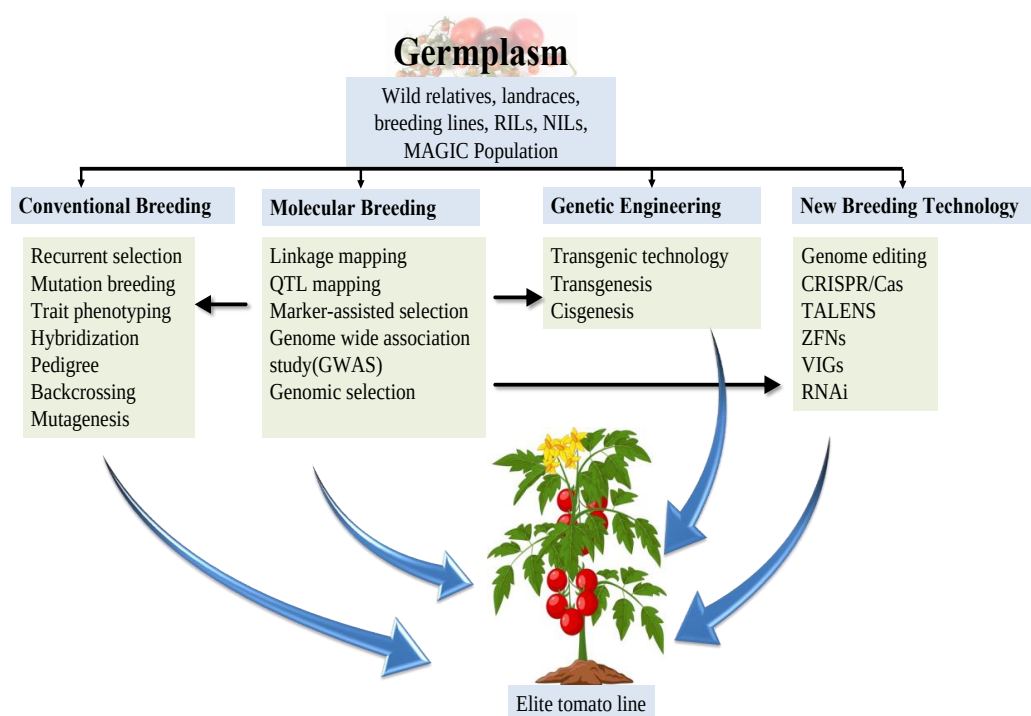


Figure 5. Proposed novel breeding tools to develop durable resistance to the Septoria leaf spot in tomatoes. Recombinant inbred lines (RILs), Near-Isogenic Lines (NILs), Multi-parent advanced generation inter-cross (MAGIC) populations, Quantitative trait locus (QTL mapping), clustered regularly interspaced short palindromic repeats-CRISPR-associated nucleases systems (CRISPR/Cas), Transcription Activator-Like Effector Nucleases (TALENs), zinc finger nucleases (ZFNs), Virus-induced gene silencing (VIGS), RNA interference (RNAi) [86,92,96–107].

It is important to note that resistance genes (R-genes) specific to a particular pathogen race may become less effective if new, more virulent races develop. Therefore, creating non-race-specific resistance through plant breeding strategies by combining different R-genes or using non-R-genes methods of genetic resistance is crucial. However, significant work is required to better understand the traits related to quantitative resistance to *S. lycopersici*. To expedite the improvement of tomatoes, additional research is needed to identify QTLs linked to *S. lycopersici* resistance, use modern selection methods, and use genomic information obtained from next-generation DNA sequencing technologies.

Plant disease resistance gene analogs (RGAs). RGAs are a group of genes linked to disease resistance and are high-priority markers for advancing host resistance [108]. It is crucial to identify known motifs such as receptor-like kinases (RLKs), receptor-like proteins (RLPs) in pattern recognition receptors (PRRs), nucleotide-binding domain, and leucine-rich repeat receptors (NBS-LRRs) or NOD-like receptors (NLRs) for R-genes [108]. This process was used to identify RGA markers and to create a user-friendly database using various bioinformatics approaches [108]. Additionally, chromosome-specific 4668 RGAs were identified in tomato, and the genes were annotated [109]. These mapped genome-wide RGAs create high-density R-genes genetic maps, developing diagnostic markers with potential for co-locating QTLs. Markers made from RGAs can be used to fine-map and clone R-genes. To develop tomato varieties resistant to *S. lycopersici* using RGAs, it is crucial to identify potential RGAs and incorporate associated SNPs.

QTL-seq mapping approach. The bulked segregant analysis (BSA) [110] approach could be a faster, more accurate, and more straightforward method for identifying markers in large populations. BSA has been employed to assess disease resistance [95]. However, it relies on an appropriate disease phenotyping index. QTL-seq is a technique that combines BSA and NGS, which has been proven effective in identifying significant QTLs [111]. However, it has limited sequencing depth and is unsuitable for large populations. Moreover, identifying major QTLs that explain a substantial portion of the observed phenotypic variation is challenging. Conventional QTL mapping and QTL-seq have identified significant QTLs in other crops [112]. This method has also enabled the identification of five key heat tolerance QTLs in tomatoes, and RNA-seq analysis has further identified crucial genes linked to these QTLs [113]. Future work may discover QTLs related to *S. lycopersici* resistance through parallel QTL mapping and QTL-seq. To identify specific genomic regions associated with target traits, NGS-based BSA-seq, which does not require parental genome sequences, has been developed and utilized to introduce new trait variations [114]. Although some wild species resist *S. lycopersici* (Table 1), such resistance is often linked to undesirable traits such as late maturity, indeterminate growth, small fruit size, and lower yield [84,95].

Genome-wide association study (GWAS). With advances in sequencing and genomic technologies, GWAS and genotyping-by-sequencing (GBS) serve as powerful tools for identifying single nucleotide polymorphism (SNP) markers [115]. GWAS is increasingly used to understand quantitative resistance in field crops [116]. For example, a 9K SNP wheat chip and GWAS analysis in a panel of 528 spring wheat accessions were used to discover SNP markers significantly associated with resistance to multiple leaf spot diseases, including *Septoria tritici* blotch of wheat. Novel QTLs were found and, subsequently, the candidate functional genes for critical agronomical traits of wheat [117]. A novel OmeSeq-qRRS (quantitative Reduced Representation Sequencing) technology for genotyping has been developed to identify potential genome-wide markers (basewisesolutions.com). Currently, we are using Ome-Seq and GWAS to analyze over 200 tomato accessions and discover potential SNP markers linked to QTL resistance to *S. lycopersici* [118]. Tomato breeders have access to SNP chips, which can aid in breeding tomatoes. However, SNP chips may not always effectively track desirable traits in unrelated tomato crosses [119]. Multiple QTLs with small but additive effects control many resistance traits worth selecting for, making it challenging to advance host resistance.

The GWAS can be enhanced through the additional application of RNA-seq analysis. RNA sequencing is a powerful tool that allows researchers to investigate and analyze how genes are turned on or off in response to pathogen attacks. It provides a comprehensive understanding of host defense mechanisms against pathogens. Many researchers combine GWAS with RNA-seq analysis to clearly understand genes activated or suppressed during host–pathogen interactions [120]. Similarly, transcription factors are crucial in orchestrating the intricate molecular responses during host defense pathways. They are proteins that regulate the expression of genes. Researchers are increasingly using bioinformatics and machine learning techniques better to understand the functions of transcription factors [104]. These methods enable efficient analysis of large datasets, pattern identification, and gene expression and regulatory network prediction. Scientists can uncover the intricate molecular mechanisms underlying host defense responses by combining RNA sequencing, bioinformatics, and machine learning approaches. These emerging technologies should provide a deeper understanding of how tomato plants defend themselves against *S. lycopersici*.

Genomic selection (GS). GS is an alternative method to MAS that is more effective for quantitatively controlled traits [119]. GS uses NGS and focuses on many markers. The prediction accuracy of GS can be improved by incorporating significant loci from GWAS and functional genes from molecular experiments as fixed effects in the GS model [121]. Genomic estimated breeding values (GEBVs) are calculated using genotypic and phenotypic data, and they predict the performance of breeding population members as parents of the following generation [122].

Overall, these genomic tools hold promise to develop molecular markers that can be used to speed up tomato breeding for resistance to *S. lycopersici*. However, there are limited studies on tomato-*S. lycopersici* interactions and potential sources of resistance to SLS. Additional research on host resistance mechanisms to SLS is required. If the assumption that a single gene controls resistance is incorrect, and several minor QTLs contribute, then genomic selection (GS) may be a practical approach for advancing tomato resistance to *S. lycopersici*.

Transgenic technology. The emerging genetic modification of tomatoes shows great potential for enhancing host resistance. Researchers can analyze and alter genes through genetic transformation to develop new and improved crop varieties. Genetic engineering enables the transfer or editing of desired traits in plants, which traditional breeding methods cannot achieve. Scientists have employed genetic modification techniques to understand the genes in tomatoes and their natural functions, leading to the development of genetically modified tomato varieties. For instance, boosting the levels of NPR1 (non-expressor of PR genes) proteins in transgenic tomato lines enhances their resistance to bacterial and fungal diseases [123]. With the identification of the genes causing both susceptibility and resistance to SLS in tomatoes, genetic transformation and gene-editing techniques may be applied to strengthen tomato resistance to SLS. To date, GMO tomatoes have not been widely accepted in the market.

CRISPR technologies. Genome editing is a cutting-edge technology with superior potential for advancing breeding strategies. Unlike traditional breeding methods, genome editing enables targeted modifications to nearly any crop genome sequence, generating novel variation and accelerating breeding efforts [124]. Genome editing relies heavily on accurate sequence information of known genes influencing host resistance to determine the target position. It has been implemented through precise sequence modifications to confer resistance to several tomato pathogens (Table 2); thus, it is a promising approach to advance SLS resistance.

The utilization of emerging genome editing tools such as zinc finger nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), and clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPR/Cas9) can provide new approaches to enhance genetic diversity in crops [125]. Scientists have introduced genetic variation from wild tomatoes into cultivated lines using CRISPR (Figure 6). This is crucial for enhancing biotic and abiotic stress tolerance, particularly in the context

of heightened concerns about climate change, to ensure the resilience and productivity of crops (Table 2).

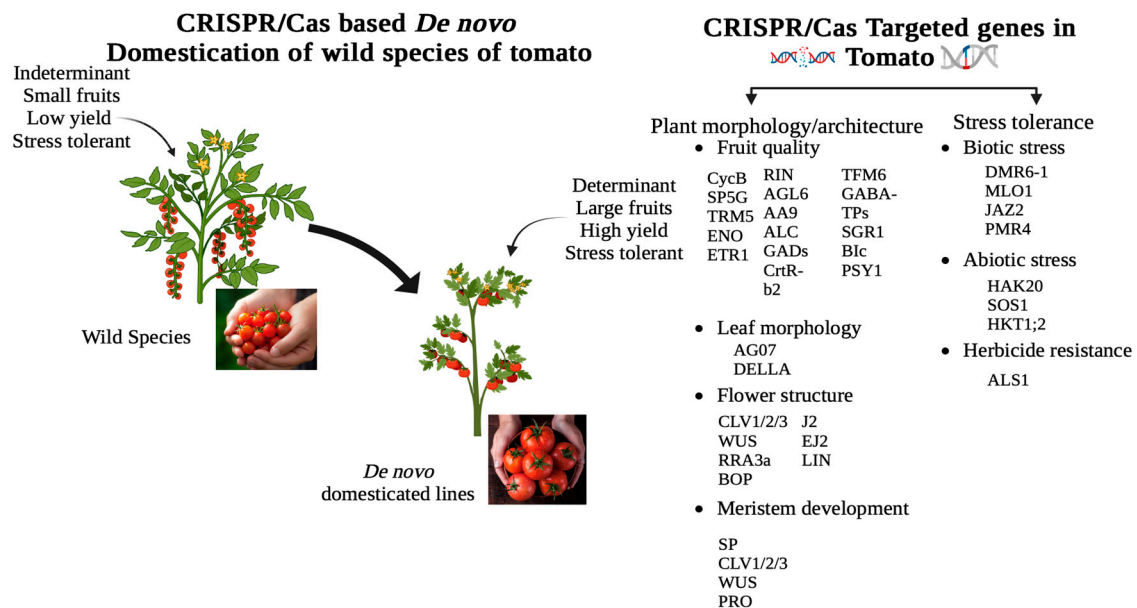


Figure 6. The implication of CRISPR/Cas-based *De novo* domestication of wild relatives of tomato and the list of genes targeted by CRISPR/Cas for improving the traits related to growth habits, fruit quality, biotic and abiotic stresses [126].

Table 2. Examples of CRISPR technology used to develop disease-resistant tomatoes.

Target Gene	Gene Function	CRISPR Process	Effects	Tomato Pathogens	Reference
<i>SlJAZ2</i>	Co-receptor of Coronatine (COR) in stomatal cells	Knock out	Prevents stomatal re-opening by COR and provides resistance to <i>Pseudomonas syringae</i>	<i>Pseudomonas syringae</i>	[127]
<i>SIDMR6-1</i>	Susceptibility gene that transforms salicylic acid (SA) into inactive form or plays a function in SA homeostasis.	Inactivation/knock out	Inactivation of the gene enhance disease resistance with increase SA levels and transcriptional activation of immune response	<i>P. syringae</i> ; <i>Xanthomonas</i> spp.; <i>Phytophthora capsici</i>	[128,129]
<i>Solyc08g075770</i>	Encodes a short transmembrane protein with potential phosphorylation and glycosylation sites.	Knock out	Knockout of the genes increased susceptibility indicating its R-gene function.	<i>Fusarium oxysporum</i> f.sp. <i>lycopersici</i>	[130]
<i>SIMAPK3</i> ; <i>SIMYC2</i>	Negative regulator of jasmonic acid (JA) signaling	Knock out	Activates defense enzymes and enhances the accumulation of reactive oxygen species (ROS)	<i>Botrytis cinerea</i>	[131]
<i>SIPLC2</i>	Susceptibility gene, triggered during xylanase infiltration (fungal elicitor) and increasing ROS generation resulting in ROS-induced cell death for fungal proliferation.	Knock out	Knockout of the gene reduces ROS and increases and reduces JA and SA response marker genes, respectively.	<i>Botrytis cinerea</i>	[132]
<i>PMR4</i>	A susceptibility gene involved in the accumulation of callose at infection sites	Knock out	Confer resistance to PM by complete lack of callose-infected leaves	<i>Oidium neolycopersici</i>	[133]
<i>SlPelo</i>	Susceptibility gene for TYLCV	Knock out	Mutation in the gene suppresses the accumulation of TYLCV and restricts the spread to non-inoculated plant parts.	Tomato yellow leaf curl virus (TYLCV)	[134]
<i>Coat protein (CP) and Rep (Replicase)</i>	TYLCV genes are involved in the encapsidation of genome and virus movement and vector recognition.	Knock out	Transgenic tomato plants show efficient virus interference with low accumulation of TYLCV DNA genome	Tomato yellow leaf curl virus (TYLCV)	[135]
<i>rgsCaM</i>	Inducible promoter and an endogenous silencer of RNAi and overexpressed after a virus attack.	Gene insertion	Efficient reduction in virus load in Cas9_sgRNA inoculated plants and the catalytically active rgsCaM promoter in the CRISPR construct	Tomato yellow leaf curl virus (TYLCV)	[136]
<i>DCL2b</i>	Small RNA involved in post-transcriptional gene silencing (PTGs) and antiviral defense against tomato mosaic virus	Knock out	Mutants with dcl2b genes show severe symptoms of viral infection under the natural and manual inoculated condition	Tomato mosaic virus (ToMV)	[137]

Table 2. Cont.

Target Gene	Gene Function	CRISPR Process	Effects	Tomato Pathogens	Reference
<i>eIF4E2</i>	Translation initiation factor 4E, susceptibility factor to genus of Potyviridae	Knock out	Shows variation in resistance against different isolates of Pepper vein mottle virus (PYMV)	Pepper vein mottle virus (PYMV)	[138]
<i>MiR482</i>	Conserved and large gene families play essential functions in regulating plant defense systems by targeting transcripts with nucleotide binding sites -leucine-rich repeat (NBS-LRR) motifs.	Knock out	Simultaneous knockout of MIR482b and MIR482c genes confer resistance to <i>Phytophthora infestans</i>	<i>P. infestans</i>	[139]
<i>SIMYBS2</i>	Regulates the ROS level and the expression level of PR genes and confers resistance to <i>P. infestans</i>	Knock out	Knockout of the gene makes the plant susceptible to the pathogen	<i>P. infestans</i>	[140]
<i>SIPMR4</i>	Susceptibility gene responsible for callose production in response to biotic and abiotic stresses	Knock out	Confers tolerance to <i>P. infestans</i> and <i>O. neolyopersici</i>	<i>P. infestans</i> ; <i>O. neolyopersici</i>	[133,141]
<i>XSP10</i> and <i>SISAMT</i>	Xylem sap protein (XSP) and Salicylic acid methyltransferase (SISAMT) both act as susceptibility factors for <i>Fusarium</i> . XSP promotes compatibility with <i>Fusarium oxysporum</i> f. sp. <i>lycopersici</i> (Fol), facilitating its colonization in tomato plant roots and contributing to disease symptom development. Meanwhile, SISAMT catalyzes the conversion of salicylic acid to methylsalicylate, thereby reducing the host's defense against multiple pathogen attacks.	Knock out	Dual-gene editing confers strong phenotypic resistance against Fol	<i>Fusarium oxysporum</i> f.sp. <i>lycopersici</i>	[142]
<i>DDTFR10/A</i>	The differentially displayed tomato fruit ripening (DDTFR) gene is induced by ethylene and classified as an ethylene response element binding protein.	Knock out	Knockout of the gene increased Fol resistance in tomato	<i>Fusarium oxysporum</i> f.sp. <i>lycopersici</i>	[143]
<i>SITOM1a</i> and <i>SITOM3</i>	Tobamovirus multiplication (TOM) susceptibility proteins interact directly with the tobamovirus replication protein, facilitating the assembly of the viral replication complex.	Knock out	Simultaneous knockout of both genes increases resistance against the tomato brown rugose fruit virus.	ToBRFV (tomato brown rugose fruit virus)	[144]

10. Conclusions and Future Prospects

Innovative approaches and advanced technologies, beyond traditional fungicides, are necessary to combat the threat of SLS in tomato production. In the short term, the focus should shift towards maximizing the use of available technologies and exploring alternative management techniques. This includes implementing more precise IPM strategies involving biological control agents (BCAs), cultural controls, and fungicides. To facilitate progress, it is crucial to develop accessible and practical techniques for phenotyping SLS resistance and expanding the discovery of genetic resistance sources. In addition, to overcome current challenges in developing resistance, the industry should prioritize the mid-term application of cutting-edge plant breeding technologies, such as CRISPR-Cas9 and advanced genomic selection methods. The objective of collaborative research projects should be to understand better the host–pathogen interactions that contribute to SLS susceptibility and identify new resistance mechanisms. To ensure that tomato production systems are resilient in the future, this effort must extend beyond SLS, addressing a range of diseases and abiotic stress factors.

The long-term goal is to integrate durable resistance into tomato production systems fully. This requires the development of solid and adaptive IPM frameworks that incorporate biological, botanical, and sustainable agronomic practices alongside host resistance. Continuous monitoring and adjustments of these systems are also essential to address the challenges posed by evolving pathogen population changes and environmental stresses. Developing predictive models and integrating AI-driven decision-making tools will be critical for achieving sustainable, profitable, and climate-resilient tomato production.

A multidisciplinary approach that prioritizes ecological stewardship, farmer engagement, and scientific innovation is essential for effective SLS management. With decisive action and a clear plan, the tomato industry can transition from reactive management practices to proactive, sustainable solutions essential for the future.

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