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Review

Multiple Foliar Fungal Disease Management in Tomatoes: A Comprehensive Approach

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Abstract: Foliar diseases are the significant production constraints in tomatoes. Among them, foliar fungal diseases in tomatoes, such as early blight (*Alternaria linaria*), Septoria leaf spot (*Septoria lycopersici*), and late blight (*Phytophthora infestans*), which is oomycetes, have higher economic significance. This paper will discuss the etiology, host range, distribution, symptoms, and disease cycle to help us understand the biology, followed by management approaches emphasizing the resistance breeding approach for these diseases. We provide an analytical review of crop improvement efforts, including conventional and molecular methods for improving these diseases' resistance. We discuss the importance of modern breeding tools, including genomics, genetic transformation, and genome editing, to improve the resistance to these diseases in the future.

Keywords: foliar fungal diseases; integrated disease management; marker-assisted selection; quantitative trait loci; resistance breeding; *Solanum lycopersicum*; tomato

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1. Introduction

Tomatoes are one of the most important vegetable crops in the world. They are produced in a more than five million ha area, producing more than 186.8 million mt of tomatoes per year globally [1]. They contribute USD 1.4 billion to the world economy per annum. Among the top 10 tomato-producing countries, China is the number one producer, followed by India and the USA (Table 1). Despite such a massive contribution to the global economy, they are affected by several biotic and abiotic factors, posing severe threats to their successful production. The biotic problems include bacteria, fungi, oomycetes, viruses, and root-knot nematodes, limiting the production of tomatoes. During infection, pathogens adopt various strategies, including delivering effector molecules or virulence factors into the host plant so that the host plant's defense becomes weak [2,3]. The defense mechanism is also activated on the host plant side, and biochemical activities occur. As a result, if the pathogens cannot grow on the host tissue, the resistance response occurs. In contrast, disease development occurs if they can establish relationships and grow successfully [4].

It is important to review the progress made in any area of research periodically. Such review helps to provide a direction for a researcher and professionals working in those areas. This review will summarize the information on foliar diseases caused by fungi (early blight, EB and Septoria leaf spot, SLS) and oomycetes (late blight, LB) in tomatoes, the biology of their causal agents, host resistance, genetics, and genomics resources available for managing these diseases. These are the major problems of the organic tomato production system in the US [5]. No such review is available in LB and SLS resistance, whereas two reviews were published in 2017 [6] and in 2021 [7] in the case of EB. A more recent review on host immunity for early blight is also available [8], which describes the role of virulence genes associated with pathogenecity, and the mechanism of host resistance. This review will be extended to the other two diseases. A literature search on the Web of Science used keywords including 'tomato', a combination of the above diseases, and

section-specific words such as breeding, genetics, nanotechnology, disease management, etc. For instance, a combination of resistance breeding, early blight, and tomato produced 63 hits. Using a combination of 'nanotechnology', early blight, and tomato produced only six hits. Replacing 'nanotechnology' with 'genome editing' produced only one hit, which was not relevant. We followed this strategy in all three diseases. We had to read the abstract to gauge the relevance of the paper for this review. We will expand the discussion to the use of modern cutting-edge tools, including biotechnology and genome editing, to expedite the genetic improvement process.

Table 1. Area planted (000 ha), total production (million mt), yield per hectare (ton/ha), and percentage of total production of tomatoes worldwide in 2022 [1].

Country	Production (Million Tons)	Area ('000 ha)	Yield (ton/ha)	World Production (%)
China	64.9	1111.5	58.4	34.7
India	20.6	812.0	25.3	11.0
Turkey	13.2	181.9	72.6	7.1
USA	12.2	110.4	110.7	6.5
Egypt	6.7	170.9	39.4	3.6
Italy	6.2	99.8	62.6	3.3
Iran	5.8	129.1	44.8	3.1
Spain	4.3	55.5	77.8	2.3
Mexico	4.1	84.9	48.7	2.2
Brazil	3.8	52.0	72.2	2.0

2. Foliar Diseases Caused by Fungi and Oomycetes

2.1. Early Blight

Early blight (EB) is one of the devastating foliar fungal diseases of solanaceous crops caused by *Alternaria* spp. Early blight is a severe disease in tropical, subtropical, and temperate zones. This disease impacts several solanaceous crops, including tomato, potato, and eggplant. The taxonomy of *Alternaria* species causing early blight is confusing with *A. solani, A. linariae*, *A. tomatophila*, and *A. alternata*. Some taxonomists consider *A. linariae* equivalent to *A. tomatophila* and *A. solani*. Although *A. solani* and *A. linariae* are indistinguishable morphologically, single nucleotide polymorphisms (SNPs) molecular markers in the second largest subunit of RNA polymerase (RPB2) may differentiate these two *Alternaria* species [9]. For this review, we consider *A. solani* and *A. linariae* (syn *A. tomatophila*) to be separate species. Collar rot, caused by *Alternaria linariae*, is sometimes mistaken for stem canker caused by *A. alternata* f. sp. *lycopersici*, a concern for coastal-grown tomatoes in California. Symptoms of *Alternaria* stem canker can appear on tomato plants' stems, leaves, and fruit. However, many commercial tomato varieties have resistance to this pathogen. No sexual stage has been reported for this fungus [10,11]. *Alternaria linariae* is a necrotrophic fungal pathogen capable of causing severe yield loss under conducive environmental conditions. Chaerani and Voorrips (2006) claim that complete defoliation can result from this disease in areas with high rainfall, humidity, and relatively high temperatures (24–30 °C) [10] When climatic conditions are favorable, the disease can cause a decline in yield of 40 to 80%. Different countries have experienced yield losses of up to 79% due to EB damage [12]. As tissues approach vegetative maturity, foliar vulnerability to EB pathogens rises, and fungal damage seems to progress from older to younger leaves from the base of the plant to the top.

Early blight is a global problem that affects tomato and potato crops everywhere. All continents are affected by early blight, common in tropical, subtropical, and temperate zones. East of the Rocky Mountains in the US, early blight in tomatoes can be problematic, but it is typically not an issue in the less humid mountain or Pacific regions [13]. The EB pathogen can affect every part of the plant and cause various symptoms depending on the crop growth stage. Small brown spots on older leaves that quickly expand are the first signs

of an infection. The lesions typically have a yellow halo around them. Dark, concentric rings with a "bullseye" look can be visible within these lesions. The leaf blight phase typically starts on the lower, older leaves and works up the plant. Similar signs on the stem and fruits can also be visible as the disease progresses. On stems, symptoms include collar rot, stem cankers, and sunken, elliptical-shaped brown lesions with a light center and concentric rings (Figure 1). *Alternaria linariae* has a broad host range, although it is reported most frequently on tomatoes and potatoes. Other members of the solanaceous crop family, such as eggplant, sweet pepper, and solanaceous weeds (such as black nightshade—*olanum pytcanthum*) are also infected by this pathogen [11,14].

Figure 1. Early blight symptoms shown by infected plants: concentric ring symptoms are seen on leaves on the left side (**A**), whereas stem girdling and spots on the right side (**B**) are caused by *Alternaria linariae* infection.

Early blight pathogens can survive on infected plant debris and soil for years and spread through contaminated seeds and transplants. New spores are produced in warm and moist conditions. Lower leaves become infected when they touch contaminated soil or when conidia splash. Germ tubes enter the host through the leaf epidermis or stomata. Germ tubes can re-grow when re-wetted so that infection can occur during alternately wet and dry periods. The time it takes for symptoms to appear depends on environmental factors, leaf maturity, and cultivar sensitivity [15]). More research is needed on the molecular mechanism of early blight infection. Each species of *Alternaria* (*Alternaria alternata*, *A. solani*, and *A. linariae* or *A. tomatophila*) produces a unique mixture of phytotoxic compounds, similar to other fungal diseases. *A. solani* and *A. tomatophila* produce altersolanol *A. altertoxin* I, and macrospores [16]. An extracellular protease is one of the many enzymes that plant pathogenic fungi produce in response to their host. These proteases are believed to play a significant role in the pathogen's growth, proliferation, pathogenicity, and survival.

2.2. Late Blight

Late blight (LB) is a severe disease that affects potatoes and tomatoes worldwide. It is caused by an oomycete called *Phytophthora infestans* (Mont.) de Bary. If left untreated, crops can be destroyed within 7 to 10 days under favorable weather conditions, making it one of the most devastating diseases. This disease mainly affects tomato plants' leaves, stems, and fruits and is spread by airborne asexual spores during the crop cycle. *P. infestans* is a

hemibiotrophic pathogen with many hosts in the solanaceae family, including tomatoes and potatoes. This particular pathogen is categorized as a heterothallic oomycete with two distinct mating types, A1 and A2. In Mexico, individuals of both mating types were commonly found, while in other parts of the world, the dominant clonal lineage was US-1 [17]. The A2 mating type isolates were first reported in Switzerland [18], and later in other Northern European countries, Japan, and Korea [19,20].

Tomatoes affected by late blight disease exhibit small, water-soaked brownish lesions along the margin of the leaves, which may have chlorotic borders (Figure 2). These lesions rapidly expand, causing necrosis in entire leaves. Under high humid conditions, the pathogen produces sporangiophores and sporangia on the surface of the infected tissue. This results in the whitish color of sporulation on the lower surface of infected leaves, characteristic of the disease. The leaf lesions coalesce and cause the foliage to appear blighted as the disease progresses quickly. While the disease primarily causes foliar blight, it can also result in black discoloration in the stem and shoulders of ripe fruits in a later stage. Infected fruits show shallow, brown, or purple lesion-like discoloration on their surface [15,21,22].

Figure 2. Late blight symptoms on leaf, stem, and fruits. Symptoms progress rapidly and can cover the whole plant within seven to ten days, showing a brown discoloration of infected tomatoes over the entire plant. The picture on the right is a resistant hybrid released as 'Mountain Rouge' (**A**), whereas the center and right are susceptible genotypes showing symptoms on the whole plant (**B**) and the fruits (**C**).

The disease cycle of *Phytophthora infestans* consists of the asexual and sexual phases. The asexual cycle is rapid and is a significant factor in disease development and epidemics in the field, while sexual reproduction leads to genetic recombination, resulting in new races [23]. The spread and epidemics of late blight in tomatoes highly depend upon the relative humidity and temperature during different stages of the pathogen's life cycle. The pathogen requires 100% RH and an optimum temperature of 24 °C to cause widespread damage in the field. *Phytophthora infestans* is a hemibiotrophic oomycete that alternates between a biotrophic and a necrotrophic phase [24]. In the biotrophic phase, it inhibits the host's immune defense and assimilates nutrients from the host tissue while secreting cytoplasmic or apoplastic effector proteins. These effectors mediate the invasion of host tissues, with extracellular effectors defending the pathogen and invading the host tissue, while intracellular effectors translocate inside the host cell to thwart the host cell's defensive mechanisms [25].

2.3. Septoria Leaf Spot

Septoria leaf spot (SLS), caused by the hemibiotrophic fungus *Septoria lycopersici*, affects tomatoes globally. It can cause defoliation and significant crop losses, especially

in the northeastern USA and Canada [26]. Only one haplotype of this fungus has been reported [27]. The fungus reproduces through conidia formed in pycnidia discharged in the rain or spray irrigation and spread through water droplets. The disease has been reported in every tomato-growing region. It occurs worldwide and is worse in damp, humid climates. All aerial sections of the plant can be infected by this pathogen, with rare incidences on fruits [28]. Although this fungus can affect tomatoes at any growth stage, symptoms typically appear on the older, lower leaves and stems when the first sign of fruit set starts under field conditions. Typical symptoms include small, round, or oval water-soaked spots on the undersurface of lower leaves that gradually turn dark in color and develop to become necrotic lesions with a tan or light grey center (Figure 3). In addition to leaves symptoms may appear on petioles, stems, and the calyx [29]. Necrotic patches on older leaves could have a chlorotic ring, a yellow halo surrounding them. Numerous circular spots can be seen on infected leaves. The old spots enlarge and frequently merge, giving a blighted appearance. Spotted leaves eventually turn yellow and die too quickly, causing early defoliation. Defoliation typically starts with the oldest leaves and can quickly move up the plant toward new growth [28].

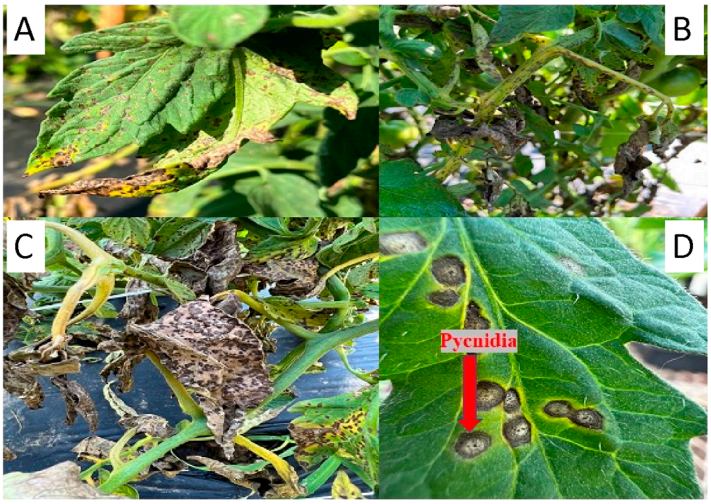

Figure 3. Symptoms on leaf and stem caused by Septoria leaf spot in tomato. Symptoms on the leaf and stem (**A**–**C**). Black color pycnidia formed on spots developed by Septoria on leaves (**D**).

The primary source of inoculum for *Septoria lycopersici* is the leaf fragments and other plant waste from infected plants that remain in the soil over winter. When the fungus gets moisture, its pycnidia develop spores. These spores can be transported to healthy tomato leaves through overhead irrigation systems, splashing rain, or insects. Once the spores reach the healthy tomato plant, they germinate, and the fungus infects the plant through stomata or by penetrating the epidermal cells directly [30,31]. There is little knowledge regarding how the pathogenicity factors of *Septoria lycopersici* and the host resistance proteins interact. However, it is believed that pathogen-secreted tomatinase may degrade alpha tomatine, which is the host's biochemical defense component, leading to infection [32]. The spores can begin to grow in as little as 48 h in the presence of moisture, and leaf spots can form within five days. Pycnidia can appear in 7–10 days. The spores are disseminated by rain or irrigation water and can survive in the soil for up to three years on infected tissue [33].

3. Common Management Strategies for Foliar Fungal/Oomycetes Diseases

Most plant diseases are managed based on five major principles of plant disease management: avoidance, exclusion, eradication, protection, and resistance. Broadly, we can manage the foliar fungal disease of tomatoes by following cultural practices, chemical control, the use of resistant varieties, and integrated pest management strategies.

3.1. Cultural Practices

Many pathogens threaten tomato plants, including foliar fungal diseases such as early blight, Septoria leaf spot, and oomycetes that cause late blight. These diseases are disseminated primarily through water and airborne pathogen particles that drop on plant leaves and infect them. These particles can come from various sources, such as adjacent alternate hosts, stray tomato crops, or diseased plant debris. Numerous practical, cultural approaches are used to tackle these diseases to reduce the entry of pathogen particles.

Field sanitation includes eliminating pathogen sources such as crop debris, weeds, and alternate hosts to avoid disease spread. Diseases frequently invade tomatoes through diseased plant debris, leftover fruit, and staking poles, which can be bleached to limit pathogen survival. Crop rotation with unrelated plants is critical for managing soil-borne illnesses produced by persistent cultivation of the same crop [34]. Planting proper crop management techniques such as balanced fertilizer application and mulching can reduce foliar diseases. Drip irrigation is preferred over sprinkler irrigation to prevent leaf moisture and fungal spore germination.

Chemical control comprises various agrochemicals, primarily as preventive measures, although it is expensive and has environmental concerns. Copper-based fungicides are widely utilized, although they are toxic to soil microbes. Synthetic pesticides such as Azoxystrobin, chlorothalonil, and others combat fungal diseases. However, their long-term use has resulted in pathogen resistance, necessitating fungicide rotation for better resistance management. In summary, field sanitation, crop rotation, correct crop management practices, and the prudent use of agrochemicals are critical cultural methods for managing foliar diseases in tomato plants.

3.2. Secondary Metabolites and Their Role in Plant Disease Management

Secondary metabolites greatly aid the control of foliar plant diseases. These secondary metabolites or organic chemicals are produced by plants for intentions other than fundamental growth and development, frequently acting as a defensive mechanism against pathogens. Secondary metabolites can function as organic fungicides or antifungal agents in the context of fungal infections [35–37]. Plants produce many secondary metabolites, such as terpenoids, phenolics, and alkaloids, which have antifungal and bacterial effects. These metabolites can stop fungal growth, interfere with their life cycles, or even attack the cell walls of fungal organisms directly when they are present in sufficient amounts in plant tissues. Several studies have explored natural alternatives for controlling specific plant diseases using secondary metabolites and organic compounds. Here is a summary of key findings.

The study on the role of secondary metabolites in disease suppression and control has a long history. Blaeser and Steiner (1999) found that only two of the 35 plant extracts they tested had an efficacy exceeding 80% against *Phytophthora infestans*. The extracts from *Potentilla erecta* (90%) and *Salvia officinalis* (83%) had the most potent antifungal effects [38]. The two plant extracts were then tested in field trials against *Phytophthora infestans* on potato plants, where they reduced disease severity and increased potato yield. Further analysis revealed that the extracts from *Potentilla erecta* can inhibit the pathogen's mycelial growth, leading to significant changes in the morphology of the mycelium. These findings demonstrate the potential of these plant extracts as effective agents against *Phytophthora infestans* and their influence on the pathogen's growth and morphology.

Khan et al. (2012) discovered that applying *Paenibacillus lentinmorbus* to tomato plants reduced the disease caused by *Alternaria solani* by 43.5% [39]. The bacteria inoculation increased the expression levels of genes responsible for encoding resistance-related proteins and plant growth factors. Key resistance-conferring genes, including *PR1*, *PR2a*, *PR2b*, *Chi3*, *Chi9*, *Pti4*, and *Pto* kinase showed higher expression. The plant hormones responsible for promoting plant growth, IAA3, and Gibberellin, showed a twofold increase in expression in the inoculated plants.

Bajpai et al. (2012) tested the effectiveness of methanol extracts from five native plant species against several plant pathogens [36]. The study found that the methanol extract of *Phytolacca americana* was highly effective against tomato gray mold and tomato late blight, with disease control rates of 85.0% and 82.1%, respectively, at a concentration of 3000 ppm. *P. americana* was also highly effective in controlling tomato late blight, achieving a disease control efficacy of 96.1%. The extract significantly reduced disease severity to 2.33% when applied to tomato plants before exposure to *P. infestans*.

Tomatoes had elevated levels of secondary metabolites, including JA hormone, after *P. infestans* inoculation. A study by Zuluaga et al. (2016) found that 348 pathways were activated, including secondary metabolite production, fatty acid biosynthesis, and degradation of various compounds [40]. The genes endo-β-1,3-glucanase (GH-17), lipoxygenase, chitinase (GH-19), and PR1 had the highest transcript abundance at 96 h after inoculation. During the transition phase, genes associated with defense were upregulated at a differential level.

Sarkar et al. (2017) used next-generation sequencing to explore how tomato plants respond to *Alternaria solani* infection [41]. They categorized genes into different groups and discovered increased genes associated with phenylalanine and phenylpropanoid biosynthesis pathways during infection. These pathways produce secondary metabolites that defend plants against pathogens. Chohan et al. (2019) found that extracts from *Allium indica*, *Allium sativum*, and *Ocimum sanctum* can reduce early blight in tomato plants [37]. The extracts effectively reduced disease rates by 62.32% and 77.42% for aqueous and methanolic extracts, respectively. The extracts from *A. indica* and *A. sativum* were found to be rich in flavonoids, saponins, terpenoids, and cardiac glycosides, which were directly correlated with their antifungal properties. *A. indica* had the highest phenolic content (56.43 mg gallic acid equivalent (GAE)/g), followed by *A. sativum* (54.25 mg GAE/g) and *O. sanctum* (53.38 mg GAE/g). The extracts were also effective against late blight and other plant-pathogenic fungi.

Bahramisarif and Rose (2019) conducted a study on the effectiveness of oak–bark compost for enhancing tomato plant growth and disease resistance [42]. They found that combining oak–bark compost with *Bacillus subtilis* subsp. *subtilis* and commercial products led to the most promising results. The combination of oak–bark compost and *B. subtilis* subsp. *subtilis* boosted plant growth and effectively reduced disease incidence in tomato plants, particularly in Phytophthora infections. Surprisingly, their research revealed that the secondary metabolite anthocyanin was negatively correlated with disease suppression. This combination showed the most significant potential for fostering improved plant growth and offering more consistent and reliable protection for tomato plants.

In a parallel study, Hernandez-Ochoa et al. (2020) demonstrated the efficacy of the liquid filtrate from *Macrolapiota sp*. in suppressing early blight in tomato plants [43]. This effectiveness was attributed to sesquiterpene lactones and quinones, which were identified as secondary metabolites and implicated in the antifungal mechanism. These compounds had been observed to have antifungal properties in previous research.

A recent study found that *Chaetomium globosum* (Cg-2) can stimulate systemic resistance against early blight in tomato plants. Cg-2 inoculation upregulated critical processes, including metabolite biosynthesis, hormone signaling, and the MAPK pathway. Jasmonic acid (JA) biosynthesis played a significant role in Cg-2-induced systemic resistance (ISR). Inoculated plants showed full activation of the salicylic acid (SA) pathway, highlighting the role of systemic acquired resistance (SAR) in Cg-2-induced systemic defense. Cg-2 treatment also improved the growth and development of tomato plants [44].

Nguyen et al. (2022) have identified seven different secondary metabolites from the culture filtrate of *A. tabacinus* SFC20160407-M11, which have shown to be effective in controlling fungal diseases such as rice blast, tomato late blight, and wheat leaf rust [45]. Two of these compounds, violaceols (also known as Phenyl ethers) and diorcinol, have demonstrated potent antibacterial activity against tomato late blight in vitro experiments. Compared to untreated controls, violaceols, and diorcinol were particularly effective in

reducing the spread of rice blasts, tomato late blight, and pepper anthracnose. Notably, diorcinol exhibited better results than violaceols I and II, showing a 62% and 50% reduction in the diseases at the same dosage, respectively, while achieving a remarkable 96% reduction in late blight. These findings suggest that the culture filtrate of *A. tabacinus* SFC20160407-M11 and its active constituents hold significant promise for developing innovative natural fungicides for agricultural applications.

Similarly, Brooks et al. (2022) identified *Xylaria feejeerisis*, an endophyte, effectively controlled early blight in tomatoes when used at 7 mg/L [46]. They identified 12 secondary metabolites, among which nine compounds, phomopsiketone B, cycloepoxydon, (R)-O-methylmellein, (3,4)-*trans*-4-hydroxymellein, (3,4)-*cis*-4-hydroxy-5-methylmellein, (3,4)-trans-4-hydroxy-5-methylmellein, 3,4-dihydro-3,4,8-trihydroxy-1(2H)-naphthalenone, sclerone, and regiolone, were identified with potential antifungal activities requiring further confirmation.

A study by Awan et al. (2023) explored the antifungal properties of both extracellular and intracellular metabolites of *Bacillus subtilis* BS-01 [47]. These metabolites were extracted using n-hexane, dichloromethane, and ethyl acetate. Concentrations over 40 mg mL^{-1} of different fractions exhibited significant antifungal activity against *Alternaria solani*, where the ethyl acetate fraction from both extracellular and intracellular metabolites exhibited the most potent inhibition of fungal biomass, followed by the n-hexane and dichloromethane fractions. In terms of extracellular metabolites, the ethyl acetate fraction contained n-hexadecanoic acid (10.10%) and octadecane (7.10%) as the most prominent compounds, while the n-hexane fraction featured triphenylphosphine oxide (TPPO, 41.40%) and dodecyl acrylate (8.60%) as noteworthy constituents, with TPPO being recognized for its antimicrobial properties. The dichloromethane fraction harbored pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl) (28.20%) and pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro-3-(phenylmethyl) (27.20%), both of which have potential as antifungal compounds. Similarly, the intracellular metabolites composition of the ethyl acetate fraction included n-hexadecanoic acid (7.73%) and n-tridecan-1-ol (6.15%) as the predominant components, while the n-hexane fraction contained octaethylene glycol monododecyl ether, pentaethylene glycol monododecyl ether, and hexaethylene glycol monododecyl ether as the most abundant compounds, all with varying degrees of antimicrobial activity. The dichloromethane fraction featured phthalic acid, butyl undecyl ester (1.07%) as the most prevalent compound, known for its antimycotic potential. Overall, the study discovered a range of organic compounds within different fractions of extracellular and intracellular metabolites derived from BS-01, with several of these compounds demonstrating significant antifungal properties. These findings suggest the potential of these metabolites for use as antifungal agents or advancing antimicrobial treatments. Esquivel-Cervantes et al. (2022) evaluated the suitability of organic products including *Bacillus* spp., and *Bacillus subtilis* for soil application, and *Reymoutria sachalinensis, Melaleuca alternifolia*, harpin αβ proteins or bee honey, and compared them against conventional treatments [48]. There was no significant difference between these two groups of treatments, indicating that the organic group of treatments was as effective as the conventional treatments when used in the greenhouse conditions [48].

3.3. Nanotechnology in Plant Protection

The application of nanotechnology to agriculture is a relatively new development. Nanomaterials are becoming increasingly popular in crop production as cutting-edge antimicrobial agents, control agent delivery tools, disease detection, and nano fertilizers to improve plant health. This is particularly true considering that nanomaterials have unique qualities such as a high surface area to volume ratio, the ability to exchange ions and chelation, enhanced reaction, unique configuration, huge ion adsorption ratio, they dissolve in water, and they are less harmful to mammalian cells than conventional antibiotics [49–51]. Additionally, they require more straightforward preparation and superior chemical stability. Because of their abundance and low toxicity, many nanoparticles are often used as

antimicrobial compounds [49]. Only Au, Cu, and Zn-based nanomaterials are drawing attention, even though several Nanomaterials are efficient against various microorganisms, including bacteria, fungi, and viruses [51–53]. While specific nanomaterials may strengthen plants' natural defenses against pathogens, others act directly as antibacterial agents. Most nanotechnology studies for controlling plant diseases have used nanoparticles made from metalloids, metallic oxides, nonmetals, and carbon nanomaterials [51]. There are numerous examples of the use of nanomaterials for the control of plant pathogens or use as antimicrobial agents, including the use of Ag colloidal against rose powdery mildew [54].

Alternaria linariae in tomatoes has been successfully treated using synthetic mesoporous silica nanoparticles [55]. Ansari et al. (2023) have reported that green nanoparticles were highly effective against early blight in tomatoes [56]. They used the silver nanoparticles synthesized using neem leaf extracts. They found it upregulates SOD, CAT, and ATX activities, reducing oxidative damage levels and improving plant growth under early blight stress conditions. Similarly, the myco-synthesized silver nanoparticles with promising antifungal effect against plant pathogenic *Alternaria solani* were discovered by Abdel-Hafez et al. (2016) [57]. Interesting fact: Endophyte nonpathogenic *Alternaria solani* strands isolated from tomato leaves were used to make the fungal extract used to make the nanoparticles. Quick detection and diagnosis of plant diseases have been achieved by using nanomaterials' capacity to conjugate with nucleic acids, proteins, and other biomolecules. Nanoparticle-based kits and sensors have recently been developed for fast disease diagnosis. Quantum dots can be employed in diagnostics since they are programmable fluorescent nanocrystals. For example, Rad et al. (2012) created a quantum dot-based nano sensor to detect *Candidatus Phytoplasma aurantifolia* in lime [58]. Similarly, Brusca (2003) also created a chip-based hybridization method that uses AgNPs to diagnose *Phytophthora* species [59]. Further, Fukamachi et al. (2019) reported using poly lactic-co-glycolic acid (PLGA) nanoparticles to encapsulate cyazofamid and develop a precise pesticide delivery system to control the *Phytophthora infestans* effectively [60].

As we know, numerous plant micronutrients are crucial for growth and protection against plant diseases. Therefore, essential micronutrients must be available for plants to grow and develop properly. Nanoparticles can be used to improve foliar availability and proper micronutrient delivery. Ali et al. (2015) synthesized Ag-based nanoparticles in combination with plant extract, sprinkled them in plants, and saw a decline in the incidence and progression of *Phytophthora parasitica* and *P. capsici* disease because of enhanced plant defense mechanisms [61]. Using foliar and soil-applied agrochemicals, adopting resistant cultivars, crop rotation, and other management techniques are examples of current control tactics. Since current methods fail to provide complete crop protection, newer, less expensive, and less harmful technologies like nanomaterials should be investigated more.

Nanotechnology deals with materials smaller than 100 nm, which can be used at the molecular level. These molecules may be Ag-based, C-based, Ce-based, Cu-based, Mg-based, Si-based, or Ti-based [62]. This technology has several applications and is being explored in agriculture. Cu-based nanoparticles were effective against early blight pathogens [52]. Some of the applications have already been developed and evaluated. For example, silver oxide nanoparticles, including early blight, were developed to manage multiple bacterial and fungal diseases in tomatoes. They were influential in suppressing development, reducing the fungal spore count, and increasing the chlorophyll content in plants [53]. In another study, mesoporous silica nanoparticles were significantly better than metalaxyl (a control or recommended fungicide) in controlling early blight in tomatoes [55] and improving the overall growth-related traits, including plant height, fresh weight, and dry weight of tomatoes.

3.4. Integrated Disease Management (IDM) for the Management of Foliar Fungal Diseases of Tomato

Integrated Disease Management (IDM) is a comprehensive approach used in crop systems to prevent and manage diseases effectively. It involves closely monitoring the health of crops and taking action as needed. IDM combines various disease management

techniques to address crop diseases, including biological, chemical, cultural, and physical methods. This approach encompasses sound agricultural practices aimed at achieving profitable crop production while prioritizing sustainability in crop health management. IDM seeks to optimize disease control by integrating diverse strategies and minimizing the environmental impact.

In tomato production, Integrated Disease Management (IDM) begins with selecting disease-resistant or tolerant tomato varieties. The approach also includes practices like optimizing irrigation to reduce leaf wetness, implementing a suitable fertilization program for healthy crop growth, maintaining the proper planting density, managing the crop canopy effectively, conducting regular disease monitoring throughout the growing season, and ensuring proper harvesting and post-harvest handling [63]. These measures collectively form an IDM system, resulting in higher yields, improved quality, and reduced environmental impact in tomato cultivation.

Integrating diverse disease management strategies has proven effective in controlling foliar diseases in tomato production. These strategies include using African marigolds as trap crops, treating seedlings with Imidacloprid as a root dip, applying neem and Pongamia cake to the soil, and using biopesticides like Pongamia soap as a spray. Additionally, plant growth-promoting bacteria have emerged as efficient and eco-friendly alternatives to chemical treatments for disease management in tomatoes. Microbes are also utilized as soil and plant inoculants in various crops, including tomatoes, showing promise in inhibiting diseases and promoting crop growth [64]. Furthermore, harnessing host plant resistance is an economically viable, technically feasible, environmentally safe, and socially acceptable approach to managing foliar fungal diseases in tomato production through Integrated Disease Management (IDM) programs [65].

3.5. Breeding and Use of Resistant Cultivars

Breeding for resistance to the early blight was initiated in the early 1940s. Resistance identified from *Solanum habrachaites* and *S. pimpinellifolium* is still useful as a source of resistance. Several public and private tomato-breeding programs have released multiple EB-resistant breeding lines and hybrids using those sources of resistance. Moderate foliar resistance derived from Campbell 1943 (C1943) has been advanced into greatly improved horticultural backgrounds, and resistant breeding lines NC EBR-2, NC EBR-3, and NC EBR-4 were released in the 1980s [66,67]. These lines are extensively used to incorporate EB resistance throughout the world. The C1943 resistance source also confers a high resistance level to the collar rot (stem lesion) phase of early blight, which is an occasional problem in western NC. A field study in 1986 showed that some of the lines identified as resistant to stem lesions in the greenhouse were also resistant to the foliar blight phase of early blight [68]. *Solanum hirsutum* PI 126445 was used as a source of early blight resistance in developing the breeding line NC EBR-1 [69]. Combining resistance from C1943 and PI 126445 sources resulted in the development and release of the breeding lines NC EBR-3 and NC EBR-4 and their F1 hybrid combination as 'Mountain Supreme' [67]. The early blight-resistant hybrid 'Plum Dandy' and its parents, NC EBR-5 and NC EBR-6, were released in 1996 [70]. The plum tomato hybrid 'Plum Crimson' and its parental lines, NC EBR-7 and NC EBR-8, were released in 2002. 'Plum Regal' and breeding line NC25P are resistant to late blight (*Ph-3* gene) and moderately resistant to early blight [71]. Another hybrid', Mountain Magic', and breeding line NC 2CELBR are resistant to both early and late blight [72]. Using the same source, we released more late blight-resistant hybrids, including 'Mountain R', 'Mountain Bebe', and 'Mountain Crown' [73–75].

Genetic resistance to LB in tomatoes has been of interest for many years. Three significant resistance genes have been identified in the red-fruited tomato wild species *S. pimpinellifolium*, including *Ph-1*, *Ph-2*, and *Ph-3*, mapped to tomato chromosomes 7, 10, and 9, respectively. *Ph-1* is a single dominant gene providing resistance to race T-0, but new races of the pathogen rapidly overcame it. *Ph-1* was mapped to the distal end of chromosome 7 using morphological markers [76]. However, no molecular marker associated with this

resistance gene has been reported. Currently, *P. infestans* race T-1 predominates, rendering the resistance conferred by the *Ph-1* gene ineffective. The resistance conditioned by *Ph-2*, a single incomplete dominant gene mapped to the lower end of the long arm of tomato chromosome 10 [77], provides partial resistance to several isolates of race T-1 [76,78]. *Ph-2* slows but does not stop the disease's progress [77]. Furthermore, *Ph-2* often needs to improve in the presence of more aggressive isolates [14,79]. *Ph-2* has been mapped to an 8.4 cm interval on the long arm of chromosome 10 between RFLP markers CP105 and TG233 [77]. A much stronger resistance gene, *Ph-3*, was discovered in *S. pimpinellifolium* accessions L3707 and L3708 (also known as LA 1269 or PI365957) at the Asian Vegetable Research and Development Center (AVRDC) in Taiwan [80]. This gene is much more helpful than *Ph-1* and *Ph-2* and confers incomplete dominant resistance to a wide range of *P. infestans* tomato isolates, including those that overcome *Ph-1* and *Ph-2* [80]. *Ph-3* has been mapped to the long arm of chromosome 9 near RFLP marker TG591a [80]. However, a combination of *Ph-2* and *Ph-3* confers strong resistance to such isolates. Several tomato-breeding programs have recently been held worldwide, including North Carolina State University, Pennsylvania State University, Cornell University, and AVRDC. The World Vegetable Center has successfully transferred LB resistance genes to fresh-market and processed tomato breeding lines or hybrid cultivars using a combination of phenotypic screening and MAS. For example, most recently, several fresh-market tomato breeding lines (e.g., NC1 CELBR (*Ph-2* + *Ph-3*) and NC2 CELBR (*Ph-2* + *Ph-3*) and hybrid cultivars Plum Regal (*Ph-3*), Mountain Magic (*Ph-2* + *Ph-3*), Mountain Merit (*Ph-2* + *Ph-3*), and Mountain Rouge) have been released by the North Carolina State University Tomato Breeding Program, USA [71,72,81,82]. Also, more breeding lines and cultivars are in the pipeline from these and other tomato breeding programs. However, more useful PCR-based markers for *Ph-2* and *Ph-3* will expedite the selection and breeding for LB resistance in tomatoes. The present study aimed to map the genes and QTL associated with late blight resistance in a tomato population derived from intra-specific crosses.

Multiple foliar fungal and oomycete disease-resistant hybrids were developed at Cornell University (CU) in collaboration with various seed companies. These hybrids combine disease resistance and fruit quality and are being marketed by seed companies in various parts of the country. For instance, Defiant, Iron Lady, and Plum Perfect were developed in collaboration with NCSU to combine the LB resistance, whereas Stellar has similar disease resistance and earlier maturity. Brandywine and Summer Sweetheart combine disease resistance and fruit quality, particularly flavor [83,84]. Using this as background information, they used three EB-resistant lines, CU151011-146, CU151011-170, and CU151095-146, as parents from the CU and two lines (OH08-7663 and OH7536) from Ohio State University (OSU) to develop mapping populations for EB resistance [83]. They identified three QTL from chromosomes 1, 5, and 9. CU151095-146 contributed the QTL-EB9, whereas OH08-7663 contributed the QTL-EB5. Resistance in CU151095-146 was derived from C1943, whereas OH08-7663 was derived from HI7998 [83,85].

Research on early blight and late blight resistance has been advanced at the Penn State University Tomato Breeding Program. It has released multiple breeding lines and hybrids, including the award-winning grape hybrid 'Valentine.' The genetic analysis and reporting at molecular breeding have been helpful for PSU and the entire tomato breeding community. For instance, the heritability estimates reported were 65 to 71%, whereas the correlation between earliness and EB resistance was $r = -0.46$ when they used the population derived from NC84173 (S) × NC39E (R) [86]. A backcross population developed between NC84173 (S) × PI126445 (R) to estimate the heritability for early blight resistance was close to 70%. They also reported a weak negative correlation ($r = -0.26$) between maturity and EB resistance [87]. Using this population, they identified ten QTL from various chromosomes, explaining 56.4% of phenotypic variance [88]. However, Zhang et al. (2003) have reported seven QTL from chromosomes 3, 4, 5, 6, 8, 10, and 11 in a population derived from the same parents (NC84173 (S) × PI126445 (R) but a different generation [89].

A summary of this information is reported by Foolad et al. (2008) [90]. A more recent molecular mapping research is summarized in Table 2.

Table 2. Quantitative trait loci (QTL) associated with early blight (EB) and late blight (LB) resistance in tomatoes were reported in various studies in the past ten years. Readers are referred to read a review by Adhikari et al. (2017), Adhikari et al. (2023) for early blight QTL [6,91].

Trait	Population	QTL	Chr	Position	LOD Score	Additive Effect	R2-Value (%)	Reference
Early blight	NC 1CELBR × Fla. 7775	*qEBR-2*	2	16.6–20.0	4.2	−1.42	3.8	[91]
		qEBR-8	8	32.4–51.3	4.2	−1.44	12.1	
		qEBR-11	11	44.1–50.9	4.0	−1.44	11.7	
Early blight	-	EB-*1.2*	1	85.0	5.7	87.9	4.9	[85]
	-	EB-*5*	5	64.4	10.4	−126.4	11.0	
	-	EB-*9*	9	66.9	24.0	12.0	26.4	
Early blight	NC EBR1 × LA2093	cLEC73K6b-CT205	2	1.1–12.2	3	−184.9	8	[92]
		cTOF19J9-TG-463	2	46.9–64.9	3.4	−197.4	8	
		EB5.1 cLEY-18H8-Ctoc20j21	5	69.4–81.5	5.6	283.2	18	
		EB6.1 TG274-TG590	6	14.8–17.3	4.6	−182.2	16	
		TG274-cLEN10H12	6	14.8–29.0	3.7	−224.2	10	
		EB9.1 TG348-cTOE10J18	9	52.8–54.6	5.1	205.6	14	
		TG343-cLED4N20	9	60.8–69.8	3	179.7	7	
Late blight	Fla. 8059 × PI 270441	02g30527779	2	11.7	0.97	−0.12	3	[93]
		02g30827526	2	13.7	1.95	−0.17	6	
			2	14.7	1.87	−0.17	6	
		09g66536514	9	114.9	9.37	−0.76	39	
		09g66864250	9	116.4	10.14	−0.78	42	
		09g67494653	9	119.3	9.54	−0.76	40	
Late blight	NC 1CELBR × Fla 7775	solcap_snp_sl_65677	6	0	2.52	0.03	2	[94]
		solcap_snp_sl_65677	6	0.01	2.52	0.03	2	
		solcap_snp_sl_11588	8	0.27	2.01	−0.15	8	
		solcap_snp_sl_22830	9	0.32	9.18	−0.33	81	
		CL016855–0847	9	0.67	41.99	−1.69	66	
		solcap_snp_sl_69978	9	0.67	42.44	−1.72	67	
		solcap_snp_sl_8807	10	0.64	4	−0.44	2	
		solcap_snp_sl_1490	12	0.01	3.1	−0.37	2	

Septoria leaf spot resistance breeding was also initiated in the 1940s [95–97]. Some of the progress made at that time is still useful to advance the SLS breeding forward. However, more progress has yet to be made toward developing SLS-resistant breeding lines and hybrids. This disease was not a priority in most of the tomato breeding programs. With climate change, the average temperature rises and gets warmer yearly. Average temperature and humidity are higher, creating a more conducive environment for the SLS. Considering the economic importance of the problem in tomato production, we have initiated the SLS breeding program. While several advanced breeding lines have been developed or are in the pipeline, we have yet to release them. Boziné-Pullai et al. (2021) investigated the local accessions and modern varieties of tomato for EB, LB, and SLS resistance under organic and conventional production systems in Hungary [98]. They found local accessions resistant to

EB, LB, and SLS, contrary to the expectations that the modern varieties may be resistant to those diseases [98].

4. Crop Improvement Efforts through Molecular and Conventional Methods

4.1. Early Blight

It is reported that multiple genes are involved in tomatoes conferring resistance to early blight (EB) [69,90,99,100]. Top emphasis was placed on improving early blight resistance in tomatoes since the systematic tomato breeding program began. There are reports on screening for early blight resistance as early as the 1940s. Those reports and genetic analyses are still valid. For instance, the source of resistance identified in *Solanum pimpinellifolium* C1943 from Rutgers University is the primary source of early blight resistance, which is still valid in the tomato breeding program. Genomic regions and QTL conferring resistance to the EB have been identified. Those QTL have been reported to explain as high as 25% of the phenotypic variance. Some of the QTL analysis research in connection with the breeding effort is presented in Section 3.4. A comprehensive review of the availability of QTL has been reported by Beattie et al. (2007) [11] and Adhikari et al. (2017) [6]. Additional novel QTL associated with EB resistance resulting from new research are presented in Table 2.

Contrary to QTL conferring resistance to EB, some studies have reported a major gene(s) to control EB resistance [101]. However, there are no follow-ups related to these studies. The need for identification of the major gene has impeded the overall breeding progress for EB resistance in tomatoes. Progress has yet to be made in EB resistance by releasing fresh-market resistant lines despite some previous lines, including NC EBR1 through 'NCEBR8', 'NC 1CELBR', and 'NC 2CELBR' [66,67,70,102]. Hybrids were also developed using these lines, growing widely in the USA and worldwide. Those hybrids include 'Mountain Supreme', 'Mountain Magic' and 'Mountain Merit' [67,72,82]. These breeding lines and hybrids are used in the US and worldwide to improve early blight resistance. The World Vegetable Center has expanded its effort to improve the early blight resistance in tomato varieties suitable for Asian and African countries [103].

Recently, Akhtar et al. (2019) evaluated an extensive list of tomatoes of 401 genotypes with diverse genetic backgrounds in Pakistan for early blight resistance using a scoring scale of 0 to 5, where 0 = no disease at all and 5 = 100% disease on the plant. The list of genotypes consisted of genotypes from NC-released breeding lines, which were found susceptible, indicating that the pathogen isolates in Pakistan may be different from NC or the resistance introduced in those lines may already be broken down or may not be effective in Pakistan. However, they found only one resistant line—'21,396', and 56 with mild resistance [104].

Singh et al. (2017) investigated the inheritance pattern of EB resistance in tomatoes. They used multiple sources of resistance from wild relatives, including *S. habrachaites*. They found a ratio for a single dominant gene in the F2 generation in only one cross (EC520061). In contrast, it was 1:2:1 in the other crosses. Regardless of the ratio, the resistance level was reasonably good. Monogenic inheritance was also reported to be derived from PI 134417. However, most of the inheritance pattern was quantitative [105].

A recent review on molecular breeding for EB resistance in tomatoes was provided [106] in a conference paper. The QTL mapping and identification of genes have not been reported in the case of EB. This is the first step towards developing molecular markers associated with any trait. Although EB QTL mapping has been reported, there is a lack of information on the major QTL or a gene conferring resistance to the EB, which is the basis of the development of molecular markers. Because of this lack of information, marker-assisted selection (MAS) has not been employed in EB resistance.

Oliveira et al. (2016) reviewed the mechanism of plant resistance induction to various diseases. They reported using salicylic acid (SA), Jasmonic acid (JA), reactive oxygen species (ROS), callose deposition, and synthesis of defense enzymes, among other compounds [107]. Tripathi et al. (2019) also conducted a detailed review of the involvement of SA in plant systemic acquired resistance (SAR) and host resistance mechanisms at the

molecular level [108]. It has been shown that SAR was induced in tomatoes by applying *Paenibacillus lentimorbus* B-30488 to suppress early blight, and it was found to reduce disease development by 45.3% [39]. A comprehensive review of early blight resistance breeding in tomatoes was recently performed by Jindo et al. (2021) [7]. They describe various aspects including host–pathogen interaction leading to disease establishment, biological cycles, climate factors, dispersal patterns, molecular research, soil factors, the role of existing forecasting models, and their application in disease management and practical disease management strategies [7].

4.2. Late Blight

There are three major genes, *Ph-1*, *Ph-2*, and *Ph-3*, conferring resistance to the late blight of tomatoes. *Ph-1* is a dominant gene, whereas *Ph-2* and *Ph-3* are co-dominant genes. These genes were identified in *Solanum pimpinellifolium*, which is cross-compatible with *S. lycopersicum*. Late blight resistance conferred by these genes is race-specific. While the gene *Ph-1* is no longer effective, a combination of *Ph-2* and *Ph-3* is still effective in conferring resistance to the existing race (Figure 4). By combining these two genes, several breeding lines and hybrids of tomatoes have been released from NC State University tomato breeding programs worldwide, including The World Vegetable Center in Taiwan. Those breeding lines and hybrids are 'NC 1CELBR', 'NC 2CLBR', 'NC 161L', 'NC 25P', 'NC 8Grape', 'Mountain Merit', 'Mountain Rouge', 'Plum Regal', 'Mountain Crown', and 'Mountain Bebe' [66,67,71,72,74,81,82,102]. Several wild accessions are resistant to the EB, including LA2157, GI 1556, LA3111, PI126445, PI390513, and PI134417, among others, as reported by Belkhadir et al. (2004) [109], in her review paper. The *Ph-3* gene was fine-mapped on the long arm of chromosome 9 [110]. This was useful for developing molecular markers and eventually cloning this gene, which encodes a CC-NBS-LRR protein [111].

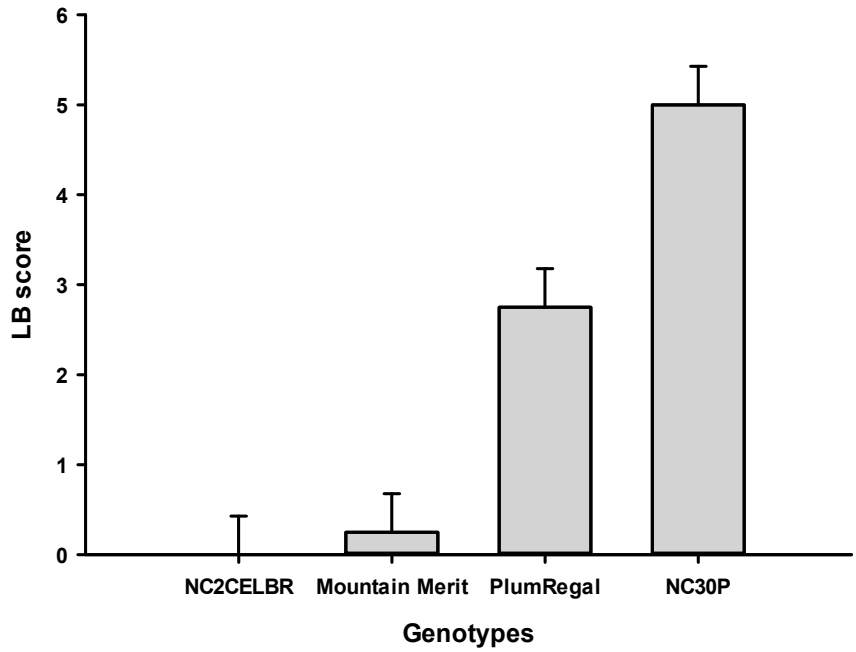

Figure 4. Tomato genotypes with various combinations of genes conferring resistance to late blight in tomatoes. In the figure, NC 2CELBR is homozygous for Ph2 and Ph3, Mountain Merit is heterozygous for *Ph-2* and *Ph-3*, Plum Regal is heterozygous for Ph3, and NC 30P does not have any resistance gene. Phenotypic data were collected in the summer of 2013 when late blight infestation was extremely high at Mountain Research Station, Waynesville, NC.

Molecular markers associated with *Ph-2* and *Ph-3* are reported in tomatoes. These markers are CAPS type, requiring restriction enzyme digestion before resolving the fragment sizes. It makes the genotyping process not only time-consuming but also costly. While

the markers are universal, we are trying to develop SCAR-type markers associated with *Ph-2* and *Ph-3*, which do not involve restriction digestion. Since the *Ph-1* gene does not have any use at present, there is little use in developing new molecular markers associated with it [112,113].

While *Ph-2* and *Ph-3* are single genes conferring resistance, QTL conferring resistance to late blight has also been reported from wild relatives [114,115]. Three QTL have been reported from chromosomes 4, 5, and 11 in the near-isogenic lines derived from a backcross population developed from *Lycopersicum esculentum* (currently *Solanum lycopersicum*) × *L. hirsitum* (currently, *S. habrachaites*). QTL on chromosome 4 mapped in an interval of 6.9 cM between TG192 and CT19,4, whereas that on chromosome 5 mapped near TG23, and that on chromosome 11 mapped to an interval of 15.1 cM between TG194 and TG400. The source of resistance traces back to LA2099 [114]. These QTL conferring resistance to LB were mapped and fine-mapped from chromosome 5 [116] and chromosome 11 separately later [117]. Near-isogenic lines were used to create sub-NIL recombinant inbred populations, one for each target chromosome region for fine mapping. From the single QTL of each chromosome, they found two and six QTL, respectively. Most of the growth chambers QTL were found to be co-located with field QTL [118]. Five QTL derived from LA1777 (*S. habrachaites*) were identified and associated with late blight resistance in terms of lesion size and were located on chromosomes 4 (two QTL), 7, 8, and 12 [119]. QTL associated with late blight resistance have also been reported from the same chromosomes derived from LA2099 (*S. habrachaites*) before [115], which has shown a high level of resistance to LB [114,117,120]. Quantitative resistance to LB has also been reported from LA716 (*S. penelli*) [121]. To make the resistance durable, Li et al. (2011), have suggested the pyramiding of resistance genes and QTL from multiple species [119].

In another study, it was reported that there were 15 QTL detected in a backcross population derived from *Lycopersicum esculentum* (currently, *S. lycopersicum*) × *L. hirsutum* (currently, *S. habrachaites*) located on chromosomes 1, 2, 3, 4, 5, and 11 [115]. Nevertheless, another QTL on chromosome 6 derived from *S. penelli* explained about 25% of the phenotypic variations [121]. Three minor QTL were found in chromosomes 6, 8, and 12 [94]. These QTL are also reported in Table 2. The World Vegetable Center has advanced late blight resistance breeding at the molecular level and developed multiple lines of tomatoes suitable for the Asian production system [122,123]. These lines can also be used in other parts of the world to introgress the resistant gene.

Four QTL located on chromosomes 1, 10, and 11 were reported in a population derived from Fla. 8059 × PI 270441 [124], and additional QTL associated with LB resistance were located on chromosomes 2, 3, 10, and 11 in a population derived from Fla. 8059 × PI 163245 [125]. These QTL were identified based on a selective genotyping approach. Five QTL derived from *S. habrachaites* (LA1777) have been reported from chromosomes 4, 7, 8, and 12 [119]. Among these five QTL, four were consistent with the previously reported QTL, and the one from chromosome 4 was novel. Four LB-resistant QTL derived from *S. pimpinellifolium* (PI270441) were identified from chromosomes 1, 10, and 11 [124]. Brekke et al. (2019) have reported two QTL derived from NC 2CELBR resistance associated with LB from chromosomes 2 and 11, which may not be novel because these QTL have already been reported elsewhere [126].

4.3. Septoria Leaf Spot

Genetic control of Septoria leaf spot resistance needs to be better understood. It has a narrow pathogen diversity. Based on our research at NC State University, there may be a quantitative mode of resistance for SLS at an early stage. However, a study conducted at Cornell University revealed that two genes may be involved in conferring resistance to the SLS, which has yet to be published. Since genetic control is unclear, the SLS-resistant breeding lines and hybrids still need to be developed. One of the most vital resources for disease-resistant germplasm is found in wild tomato species. Of the 13 wild species of tomato (*Solanum* L. section *Lycopersicon* [Mill.]) [127], SLS resistance has been discov-

ered in varying degrees in *S. pimpinellifolium*, *S. chilense*, *S. habrochaites*, *S. peruvianum*, and *S. pennelli* [128–130], with the best source of resistance found in *S. habrochaites* and *S. peruvianum* [128]. Unfortunately, crossing between cultivated tomatoes and wild species is difficult. When it can be achieved, the resulting SLS resistance in the progeny is often linked with traits unfit for commercial production [90]. A study exploring the SLS resistance of various *Solanum* accessions found that cultivated tomatoes (*S. lycopersicum* and *S. lycopersicum* var. *cerasiforme*) were the most susceptible accessions tested. Only one cultivated tomato accession was found to be moderately resistant: *S. lycopersicum* var. *cerasiforme* (CNPH-0633), and it crosses readily with other cultivated varieties [96]. Poysa and Tul (1993) offer a detailed list of partially SLS-resistant accessions to be explored in potential breeding work [130].

The SLS resistance in tomatoes is thought to be primarily qualitative, with several QTL supplementing the resistance of a single gene. In 1945, SLS resistance was reported to be significantly affected by a single dominant resistance gene called *Se.* A chromosome position for *Se* has yet to be determined [95]. Joshi et al. (2015) reported that *Se's* dominance was incomplete, although it was suggested that this could have resulted from using a parent not entirely susceptible to SLS [97]. Cornell University has been trying to determine if homozygous plants for the *Se* gene are more resistant than heterozygous plants [131].

A study conducted in Brazil evaluated a collection of 124 accessions for the SLS under greenhouse conditions. They found that ten accessions were highly resistant (HR), whereas 33 were classified as resistant (R), and the rest of the accessions were susceptible [128]. Field experiments verified the greenhouse observations using only the HR and R sub-set of accessions. Five new sources with high resistance levels were found in *S. peruvianum* accessions, including PI-306811, CNPH-1036, LA-1910, LA-1984, and LA-2744 [128].

No major gene or QTL associated with the SLS resistance in tomatoes are reported. Because of the lack of this information, molecular breeding has yet to be realized for SLS. We will map the QTL associated with the SLS in our program now. We are optimistic that we will be able to identify major QTL and eventually develop molecular markers associated with this critical disease.

Only a few tomato cultivars have been released, claiming SLS resistance. Some cultivars with good SLS resistance are 'Iron Lady', 'Stellar', 'Summer Sweetheart', and 'Plum Perfect'. The cultivars mentioned above have some degree of tolerance/resistance to several other diseases, such as late blight and early blight [83,84,131].

5. Potential to Improve Using Modern Tools

5.1. Genomic Resources

The tomato is one of the well-studied crop plants for its genomics. Its whole genome sequence was published in 2012 [132]. The total estimated number of genes in tomatoes is around 34,075. These genes have been annotated for their gene ontology and gene function. This information is summarized and presented in various resources, including online databases such as www.solgenomics.net, https://solgenomics.net/organism/Solanum_lycopersicum/genome (accessed on 4 January 2024), http://ted.bti.cornell.edu/, http://www.kazusa.or.jp/tomato/ (accessed on 4 January 2024), http://www.g2p-sol.eu/, http://www.kazusa.or.jp/jsol/microtom/ (accessed on 4 January 2024), https://tomatoma.nbrp.jp/, and review papers (accessed on 4 January 2024) [133]. Gene expression data with various treatment combinations have been generated, including biotic and abiotic stress treatments [134–137]. QTL mapping populations, QTL and genes associated with various traits, and eventually molecular markers are also available. Various portals report this information, including genes, gene expression, micro RNAs, different marker systems, and quantitative trait loci (QTL) analysis. Molecular markers include Amplified fragment length polymorphism (AFLP), Cleaved amplified polymorphic sequence (CAPS), Restriction fragment length polymorphism (RFLP), sequence characterized amplified region (SCAR), single nucleotide polymorphism (SNP), and simple sequence region (SSR). Among different reporting portal systems, Sol Genomics Network (www.solgenomics.net) (accessed on

19 December 2023) is the most informative portal. It has much information on various aspects, including biotic and abiotic stress conditions. The Tomato Genetics Resource Database (TGRD), consisting of similar information, was developed before. However, it is no longer active now [138]. However, major genes and molecular markers associated with EB and SLS are unavailable for marker-assisted selection. With the availability of next-generation sequencing facilities for lower costs, most programs are inclined to use SNPs now [139–141]. Gene expression analysis data have been generated for various tomato pathogens by inoculating the resistant and susceptible tomato genotypes and collecting tissue samples at different time points [142–144]. Performing RNA-seq analysis and gene ontology analysis, we can obtain a list of upregulated and downregulated genes and their association with various proteins. RNA-seq analysis provides information on differential gene expression and the extraction of SNP molecular markers, which can eventually be used for QTL mapping [143]. Casa et al. (2008) revealed that early infection occurs in potatoes among three species, including potato, tobacco, and tomato, when inoculated with *Phytophthora infestans* [145]. They also found that gene expression pattern was the same trend, i.e., defense-related genes, such as reactive oxygen species (ROS), were early expressed. There were some common genes among the three species. This type of research concerning EB, LB, and SLS in tomatoes is yet to be investigated in detail. Lu et al. (2021) conducted an RNA-seq analysis inoculating with *Phytophthora infestans* potato, tobacco, and tomato and collecting tissues at 12 and 24 h after inoculation. They found some specific genes and common genes differentially expressed due to the *P. infestans* inoculation [146]. This is an essential database for studying gene expression and identification associated with late blight resistance.

An updated tomato reference genome was published by Wang et al. (2016) [123]. This study has compared the *S. lycopersicum* Heinz1706 and *S. pimpinellifolium* LA2093. Moreover, comprehensive reference genomes are being reported by Pan-genome analysis to cover all available genes. More SNP molecular markers are being developed using cultivated and wild relatives, which will help map gene identification and cloning [147,148].

5.2. Genetic Transformation

Genetic transformation has been an essential tool for crop improvement, including crop yield, quality, and disease resistance [149]. The tomato was one of the first crop plants to transform and improve fruit quality. Since then, several traits have been improved. In this series, the *rolB* gene from *Agrobacterium rhizogenes* was introduced into *Agrobacterium tumefaciens*, and eventually, tomato Rio Grande was transformed. When phenotypic traits, including early blight resistance, were monitored, the disease incidence ranged from 4.17% to 25%, whereas disease severity ranged from 1.75% to 16.75%, significantly less than control values [150]. This indicated that early blight could be managed using genetic transformation. Khan et al. (2011) transformed tomatoes by fusing *miR4026*, and nucleotide-binding leucine-rich repeat (NB-LRR) revealed that *miR4026* negatively regulates the resistance to early blight caused by *Alternaria solani* in tomatoes [151]. This information is vital for developing early blight resistance by genetic transformation or genome editing targeting *miR4026*. Tomato transformation protocols for various purposes are available [152,153]. Genetic transformation and the RNA-seq approach were used to verify the role of the *miR6024* gene conferring resistance to early blight [154].

5.3. Genome Editing

Genome editing is the technique by which DNA mutations in insertion and deletion (InDels) or base substitutions are introduced to create an organism with a new or modified product [133,155,156]. There are different types of genome editing methods, as described below.

The Zinc-finger nuclease-based genome editing approach utilizes the synthetic restriction enzymes' Zinc-finger nucleases, which have DNA-binding domains that specifically bind three base pairs at the target sites. Three base-pair specificities can target a specific

amino acid and modify the amino acid of interest, ultimately leading to changes in the protein of interest [157]. It has broader applications in crop improvement.

TALEN-based genome editing includes the role of tandem repeats for the specificity of the protein domain, based on which the development of the chimeric genome editing tool known as transcription factor-like effector nucleases (TALEN) was developed. The mechanism of TALEN-based genome editing is basically via the disruption of the effector-binding element of the S-gene promoter, which eventually impairs the comparable molecular interactions between the effector and the target S-gene [157].

Oligonucleotide-directed mutagenesis (ODM) is another genome editing tool in which 20 to 100 long base pairs are identical to the target sequence except in a single nucleotide where the intended point mutation is required. The oligonucleotide-directed host DNA repair system introduces the mutation that disrupts the target gene's function. This process introduces the desired single nucleotide mutation into the target genome, resulting in the expression of a novel trait or function following subsequent regenerations by tissue culture or classical plant breeding [158,159].

CRISPR/Cas-based genome editing has recently become the most popular and has been adopted to manipulate the genome of many crop plants to achieve various breeding objectives. The components for genome editing using the CRISPR/Cas-based method are the DNA endonuclease *Cas9* protein and a customizable single-stranded guide-RNA. Once the target DNA sequence is hybridized with the complementary sgRNA, high-fidelity *Cas9* triggers dsDNA breaks [157,160].

The concept of genome editing of the susceptible gene (S-gene) has emerged and is practiced in some of the diseases in tomatoes. A summary of all those disease resistances achieved by genome editing is presented by Barka and Lee (2022) [157]. They discuss the early blight and Septoria leaf spot of the tomato. In a separate study, tomato plants were transformed with *Agrobacterium rhizogenese* with the *rolB* gene. They assessed the phenotype for early blight and insect resistance, although the mode of action of *rolB* is mainly unknown. Tomato plants were transformed using *miR482b* and *miR482c* by using the *CRISPR/Cas9* approach to enhance the late blight resistance [159].

6. Future Prospects

Foliar fungal diseases, early blight, Septoria leaf spots, and late blight (caused by oomycetes) are still the primary threats to tomato production worldwide. There are novel resources available to manage these diseases, including nanotechnology, breeding, genetics, genomics, genome editing, and biotechnology. While some genetic resources have already been utilized to manage some of the above diseases, such as early blight and late blight, other resources are yet to be used to manage these diseases better. For MAS to be employed effectively, it should be mapped precisely in the genome of the tomato. Early blight and Septoria leaf spot resistance should be mapped precisely, and reliable molecular markers should be developed to employ the MAS for these diseases. Genomic resources developed from gene expression analysis are beneficial for gene identification. Gene expression data on EB and SLS still need to be included. Future experiments in this direction will help generate the expression data and fill the gene identification gap. Depending upon their mode of action, these genes can eventually be used in genetic transformation or genome editing. Genome editing can be exploited on host resistance or to understand the pathogen's virulence. These resources are likely to be used for the integrated management of EB, LB, and SLS as required. Additional resources, including cultural management, use of secondary metabolites, and nanotechnology described in this paper, can be useful for organic tomato growers.

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