

Review

Molecular Insights into Powdery Mildew Pathogenesis and Resistance in Cucurbitaceous Crops

Magdalena Pawełkowicz ^{1,*}, Agata Głuchowska ¹, Ewa Mirzwa-Mróż ², Bartłomiej Zieniuk ³, Zhimin Yin ⁴,
Czesław Zamorski ² and Arkadiusz Przybysz ⁵

¹ Department of Plant Genetics, Breeding and Biotechnology, Institute of Biology, Warsaw University of Life Sciences-SGGW, 159 Nowoursynowska Str., 02-776 Warsaw, Poland; agata_gluchowska@sggw.edu.pl

² Division of Plant Pathology, Department of Plant Protection, Institute of Horticultural Sciences, Warsaw University of Life Sciences-SGGW, 159 Nowoursynowska Str., 02-776 Warsaw, Poland; ewa_mirzwa-mroz@sggw.edu.pl (E.M.-M.); czamorski179@gmail.com (C.Z.)

³ Department of Chemistry, Institute of Food Sciences, Warsaw University of Life Sciences-SGGW, 159C Nowoursynowska Str., 02-776 Warsaw, Poland; bartlomiej_zieniuk@sggw.edu.pl

⁴ Plant Breeding and Acclimatization Institute—National Research Institute in Radzików, Młochów Division, Department of Potato Genetics and Parental Lines, 19 Platanowa Str., 05-831 Młochów, Poland; z.yin@ihar.edu.pl

⁵ Centre for Climate Research SGGW, Warsaw University of Life Sciences—SGGW, 02-787 Warsaw, Poland; arkadiusz_przybysz@sggw.edu.pl

* Correspondence: magdalena.pawelkowicz@sggw.edu.pl

Abstract

Powdery mildew, predominantly caused by *Podosphaera xanthii* and *Golovinomyces orontii*, presents a major constraint to cucurbitaceous crop production worldwide. Despite intensive research, the complex interplay between pathogen virulence factors and host immune responses remains only partially understood. Recent advances in genomics, transcriptomics, and gene editing technologies have shed light on key molecular mechanisms underlying host susceptibility, quantitative resistance, and potential durable control strategies. In this review, we summarize the biology of powdery mildew fungi infecting cucurbits, the latest findings on pathogen effectors, plant defense signaling, and the genetic basis of resistance. We also discuss novel breeding and biotechnological approaches for durable powdery mildew resistance and outline future directions for integrative disease management strategies.

Keywords: disease resistance; plant immunity; integrated disease management



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1. Introduction

Cucurbitaceous crops, including cucumbers (*Cucumis sativus*), melons (*Cucumis melo*), squashes (*Cucurbita* spp.), and watermelons (*Citrullus lanatus*), are globally significant for their economic value and nutritional contributions. These crops are extensively cultivated across diverse agroecological zones and are an essential component of both subsistence and commercial agriculture. Their production supports food security and provides livelihoods for millions of smallholders and commercial farmers worldwide. However, the productivity and sustainability of cucurbit cultivation are continually challenged by various biotic stresses, the most predominant of which is powdery mildew (PM) [1–8].

Powdery mildew leads to significant economic losses in cucurbit production worldwide due to decreased yield quality and quantity, increased fungicide application costs, and reduced marketability of infected crops. PM infections consequently result in substantial

yield losses and diminished fruit quality. In cucumbers, for example, PM is recognized as one of the most destructive diseases, with outbreaks causing significant economic losses in both open-field and protected cultivation systems [5,9]. Similarly, in pumpkins (*Cucurbita pepo*), PM is a major cause of production losses worldwide, highlighting its impact on various cucurbit species [8,10]. In Florida, disease outbreaks have caused up to 34% yield loss in watermelons [11,12] and occur in approximately 70% of the squash acreage [13,14]. In Illinois, CPM is the most common and destructive in commercial pumpkin and squash fields and on greenhouse-grown cucumbers. It can cause yield losses from 10 to 20% where control measures are not practiced [15]. In some Indian districts, the incidence of disease ranged from 20.1% to 47.28% on various cultivars [16,17]. The traditional management of PM has relied heavily on the application of chemical fungicides. While this approach is effective to some extent, it poses several challenges, including the development of pathogen strains that are resistant to fungicide, environmental contamination, and potential health risks to consumers and agricultural workers. Furthermore, frequent and intensive fungicide use increases production costs, thereby affecting the economic viability of cucurbit farming. These limitations highlight the urgent need for sustainable and environmentally friendly disease management strategies [1,2,18].

Breeding for genetic resistance to PM offers a promising alternative to chemical control. However, developing resistant cultivars is complicated by the pathogen's high genetic variability and adaptability, which can result in resistance breaking down over time. Therefore, understanding the molecular mechanisms underlying host resistance is critical for developing durable resistance strategies. Recent advances in genomics and molecular biology have facilitated the identification of key genes and pathways involved in PM resistance. For instance, genome-wide association studies (GWASs) on cucumber have revealed loci that are significantly associated with natural variations in PM resistance. These include the *CsGy5G015960* gene, which encodes a phosphate transporter that is involved in resistance mechanisms [9]. Furthermore, studies have emphasized the significance of *Mildew Locus O* (*MLO*) genes in cucurbits, revealing that loss-of-function mutations can provide long-lasting resistance to PM [19].

Despite these advances, the molecular basis of PM resistance in cucurbits remains poorly understood. Further research is needed to elucidate the complex interactions between host plants and PM pathogens, including the identification of resistance genes, signaling pathways, and defense responses. This knowledge will be crucial in guiding breeding programs that aim to develop cucurbit cultivars with durable and broad-spectrum resistance to PM. The aim of this is to summarize the latest insights into the molecular mechanisms of PM pathogenesis and host resistance in cucurbitaceous crops, highlighting recent discoveries and identifying future research directions essential for sustainable disease management.

2. Etiology and Biology of Powdery Mildew Pathogens

2.1. Major Causal Agents in Cucurbit and Pathogen Distribution

Cucurbit powdery mildew (CPM) is caused by the obligate biotrophic fungi, mainly *Podosphaera xanthii* (Castagne) U. Braun and Shishkoff (syn. *Podosphaera fusca* (Fr.) U. Braun and Shishkoff), which was previously named *Sphaerotheca fusca*, *Sphaerotheca fuliginea* f. *cucurbitae* Jacz., and *Golovinomyces orontii* (Castagne) V.P. Heluta (previously *Golovinomyces cichoracearum* (DC) Heluta) [20,21]. These pathogens belong to the Kingdom Fungi, Phylum Ascomycota, Class Leotiomycetes, Order Erysiphales [20,22].

P. xanthii is the dominant pathogen in North America [23] and South America [24]. It is reported in Africa (Egypt, Libya, Morocco) [25–27], Asia (Israel, Turkey) [28,29], and Europe (southern France, Greece, Spain, Germany, Czech Republic, northern Italy, Ukraine, Hungary, Bulgaria) [30–37].

G. orontii occurs in temperate and colder regions. Both pathogens occur in Central Europe, either separately or together [19,33,38,39]. These pathogens may be present in the same locations and on the same cucurbit host. *G. orontii* may dominate until summer, after which it can be replaced by *P. xanthii*. This could be attributed to the lower temperature optimum of *G. orontii* [40,41].

Unfortunately, there are only a few detailed biogeographic studies on the distribution and dynamics of individual CPM species on a large-scale level [33,41–45].

2.2. Symptoms

Infections typically begin on the lower, older leaves and progress upwards. The earliest symptoms are small, circular, white, powdery fungal spots (Figure 1a,b) on both upper and lower surfaces of the leaves [46,47]. These spots are fungal colonies that consist of fungal mycelia and chains of conidia [19,32,48]. As the disease progresses, these white colonies enlarge and merge, forming large patches (Figure 1c) that can cover the entire leaf surface (Figure 1d), including the petiole and stem [46,47,49]. As the infection develops, chlorotic (yellow) areas form around the fungal colonies (Figure 1e) due to reduced photosynthetic capacity [19]. Severely infected leaves ultimately become necrotic (Figure 1f) and fall off prematurely, thereby weakening the plant's vigor and reducing its yield [32,46,48]. Although the fungus rarely infects the fruit directly, reduced foliage coverage can result in malformed, undersized, or sunburned cucumber fruits [32,50]. This results in poor ripening, reduced sugar accumulation and lower flavor quality, as well as a decreased shelf life [46,47,49].

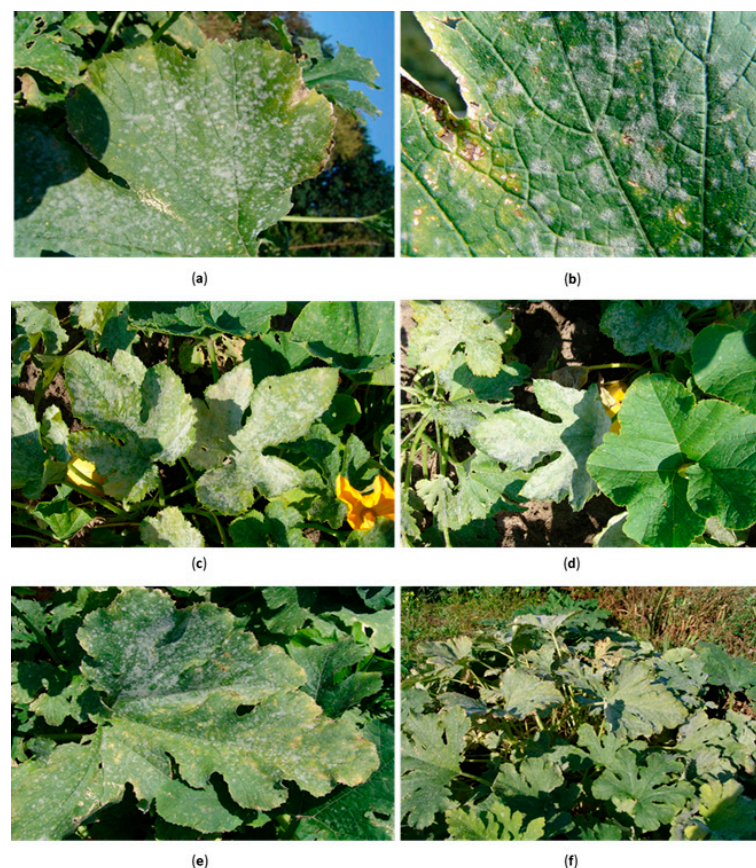


Figure 1. (a) Initial symptoms of infection in the form of small, round spots on the pumpkin leaf; (b) magnification; (c) enlarged and merged spots on the leaves; (d) whole leaf surface covered with white external mycelium with sporulation; (e) leaf with yellow discoloration; (f) first necrosis on the leaf edges. Photo Zamorski C.

2.3. Biology, Lifecycle, and Environmental Conditions for Infection

2.3.1. Overwintering

In cooler climates, pathogens can survive as chasmothecia (sexual fruiting bodies), but this is rare, because cucumber plants typically undergo senescence or are removed at the end of the season. In the case of PM on cucumber, the sexual stage has rarely or never been observed in most important cucurbit-growing areas [51,52]. The chasmothecia of these two cucurbit PM species are brown, have myceloid appendages and can be distinguished based on the size and number of asci. Chasmothecia of *P. xanthii* are (70–)80–110(–115) μm in diameter and contain 1 ascus with (6–)8 hyaline ascospores (mostly immature) while *G. orontii* are 95–150 μm in diameter with 5–14 asci containing 2–3 ascospores [20,32,38]. More commonly, these fungi survive in the form of mycelium or conidia on living plant hosts, as well as on volunteer cucurbit hosts or weeds in warm regions [32,47].

2.3.2. Infection

Primary infection occurs in the spring or early growing season. Conidia are dispersed by wind to cucumber plants [20,32,46]. Conidia do not require rain and free water for germination [20,46,53], but high humidity favors their development [54,55]; however, infection can take place in as low as 50% RH. Infection can occur at temperatures ranging 10–32 °C [53]. According to Trecate et al. [29], optimal temperatures for *P. xanthii* and *G. orontii* conidia germination were 24.4 °C and 17.9 °C, respectively. Depending on the temperature, the first symptoms can appear 3–5 days after infection [53]. Symptom expression is suppressed at temperatures >35 °C, particularly for *P. xanthii* [29].

2.3.3. Appressoria and Haustoria Formation

When conidia land on the leaf surface, they germinate into a germ tube and form lobed appressoria (a specialized infection structure). From the appressorium, the fungi form a narrow infection hypha that penetrates the epidermal cells. Inside of these, the fungi form haustoria, which are specialized feeding structures that extract nutrients from host cells without cell wall degradation [32,38,56].

2.3.4. Sporulation

The fungi reproduce rapidly by forming new chains of conidia on upright conidiophores that emerge from the mycelium. These conidia lead to secondary infection. *P. xanthii* produces long, straight conidiophores with catenescant conidia (in long chains). Conidia are ellipsoid–ovoid to doliiform, measuring 24–45 μm long and 14–22 μm wide. Fibrosin bodies are present inside conidia. *G. orontii* forms catenescant conidia that are ellipsoid–ovoid to doliiform–subcylindrical in usually short chains measuring 25–40 $\times$ (10–)15–23(–25) μm . They lack fibrosin bodies inside them and have curved foot cells [20,38,41,48]. These secondary conidia are dispersed by the wind onto new leaves or neighboring plants. The lifecycle of PM pathogens is illustrated in Figure 2.

This polycyclic nature enables powdery mildew to cause rapid and severe epidemics under favorable conditions [47,57]. The disease usually becomes visible during mid to late summer, particularly in warm, dry weather as this facilitates the rapid development and spread of spores via the wind [49].

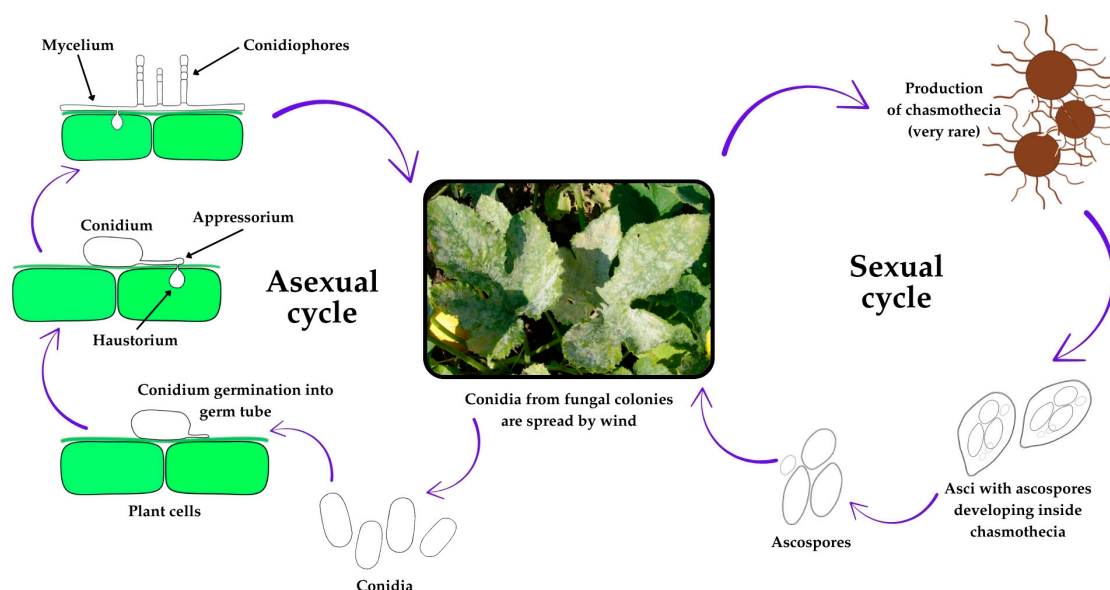


Figure 2. Lifecycle of *G. orontii*, a powdery mildew fungi, illustrating both asexual and sexual reproduction (according to [32]).

3. Molecular Mechanisms of Pathogenesis

3.1. Pathogen Effectors and Host Manipulation

Secreted effector proteins target plant immunity. In silico prediction revealed a total of 87 putative effector candidates, 65 of which had their analogs and the remaining 22 were novel ones, from a recently sequenced *P. xanthii* isolate (named YZU573) [58]. A previous study predicted 53 secreted effector protein (CSEP) candidates in *P. xanthii* based on transcriptomic data [59]. Some of these CSEPs showed elevated expression at the initial 24 h after inoculation, when the primary appressoria are mostly formed, consistent with a putative role in pathogenesis. While some effector proteins secreted by the biotrophic fungi may induce plant defense responses, others may suppress defense responses, causing disease [60–62]. Examples of the pathogen-associated molecular patterns (PAMPs) and the effectors of cucurbit powdery mildew pathogen *P. xanthii* are shown in Table 1.

Table 1. Examples of the pathogen-associated molecular patterns (PAMPs) and the effectors of cucurbit powdery mildew pathogen *Podosphaera xanthii*.

PAMP	Effector	Chemical Nature of the Effector	Function of the Effector in Host Plant	Host Putative Target of Fungal Effector	References
NA	53 CSEPs, 87 putative effector candidates	Containing the N-terminal conserved motif Y/F/WxC, with the WxC motif more abundant	<i>P. xanthii</i> pathogenesis; elevated expression at the beginning of the infection process at 24 hpi, when the primary appressoria are mostly formed.	NA	[58,59]
NA	PEC019 (PxPLBE1)	Phospholipid-binding protein	<i>P. xanthii</i> pathogenesis; elevated expression during the early stage of pathogenesis at 24 hpi. Modulation of plant cell membrane organization.	Targeting host-cell plasma membrane	
NA	PEC032 (PxMLE1)	α -Mannosidase	<i>P. xanthii</i> pathogenesis; elevated expression during the early stage of pathogenesis at 24 hpi. Host-cell glycosylation	Interaction with α -mannose	[63]
Cellulose	PEC054 (PxCLBE1)	Cellulose-binding protein	<i>P. xanthii</i> pathogenesis; elevated expression during the early stage of pathogenesis at 24 hpi. Sequesters cellulose fragments (cellopentaose), preventing cellulose recognition by the plant.	Suppression of cellulose-triggered immunity	

Table 1. Cont.

PAMP	Effector	Chemical Nature of the Effector	Function of the Effector in Host Plant	Host Putative Target of Fungal Effector	References
Chitin	PxLPMO (PHEC27213)	Lytic polysaccharide monoxygenases containing a putative chitin-binding domain 3 located from amino acids 115 to 128	Binds and catalyzes colloidal chitin and chitooligosaccharides; suppression of chitin-triggers immunity during haustorium development.	May indirectly target putative melon homologs of plant chitin receptors	[64–68]
Chitin	PxCDA	Chitin deacetylases	Converts chitin into chitosan by hydrolyzing the <i>N</i> -acetamido group in <i>N</i> -acetylglucosamine units. Chitosan has reduced affinity for plant chitin receptors; suppression of chitin signaling by avoiding recognition. Degrades chitin fragments. The degraded chitin oligomers exhibit reduced affinity for plant chitin receptors, preventing the activation of chitin-triggered immunity.	May indirectly target putative melon homologs of plant chitin receptors	[65,67–69]
Chitin	PxEWCAs	Chitinase		May indirectly target putative melon homologs of plant chitin receptors	[65,67,68,70]
Chitin	PxCHBE (PxCDA3)	A truncated version of chitin deacetylase resulting from an alternative splicing of the <i>PxCDA</i> gene, which lacked most of the chitin deacetylase activity domain but retained the carbohydrate-binding module.	Bands to the chitin oligomers, preventing activation of the chitin signaling, localizing in plant papillae where chitin is densely accumulated at pathogen penetration sites.	May indirectly target putative melon homologs of plant chitin receptors (e.g., CEBiP, CERK1)	[65,67,68,71]
NA	CSEP30, CSEP47, CSEP48	Secreted fungal protein	Induces cell death in cucumber.	Interact with CsSGR in susceptible cucumber genotype S6 and the mutant Csgsr (Q108R) in resistant cucumber genotype Gy14	[19]
	CSEP30 ^{ASP}	Mature form of the secreted fungal protein	Induces dry necrotic lesions on the abaxial surfaces of leaves and defense response.	Interacts with Csgsr in resistant cucumber genotype Gy14	

CEBiP: Chitin elicitor-binding protein. CERK1: Chitin elicitor receptor kinase. CSEP: Candidate secreted effector protein. CSEP30^{ASP}: The mature form of CSEP30 (lack of the signal peptide). CsSGR: Cucumber STAY-GREEN. Csgsr: Cucumber mutant STAY-GREEN. hpi: Hour post-inoculation. NA: Not available. PEC: *Podosphaera xanthii* effector candidate. PHEC27213: The unigene PHEC27213 selected from the *Podosphaera xanthii* haustorial transcriptome, the most highly expressed haustorium-specific gene encoding a secreted protein. PxCDA: *Podosphaera xanthii* chitin deacetylase. PxCHBE: *Podosphaera xanthii* chitin-binding effector. PxCLBE1: *Podosphaera xanthii* cellulose-binding effector 1. PxEWCAs: *Podosphaera xanthii* effectors with chitinase activity. PxLPMO: *Podosphaera xanthii* lytic polysaccharide monoxygenases. PxMLE1: *Podosphaera xanthii* α -mannosidase-like effector 1. PxPLBE1: *Podosphaera xanthii* phospholipid-binding effector 1.

Several effectors from the cucurbit powdery mildew pathogen *P. xanthii* are involved in the suppression of chitin-triggered immunity by preventing the recognition of chitin [64,65,69–72]. Chitin is a major component of fungal cell walls, and chitin oligosaccharides are well-known PAMP elicitors, which are capable of activating PAMP-triggered immunity (PTI) [64,66]. Polonio et al. [64] identified a highly expressed, haustorium-specific effector lytic polysaccharide monoxygenase (LPMO) from *P. xanthii*, PxLPMO, which was able to bind and catalyze chitooligosaccharides, thus contributing to the suppression of plant immunity during haustorium development. Silencing of the *PxLPMO1* gene by *Agrobacterium tumefaciens*-mediated host-induced gene silencing assay reduced *P. xanthii* haustorial counts and fungal biomass, and activated a strong accumulation of reactive oxygen species (ROS), including hydrogen peroxide (H₂O₂), suggesting the likely activation of chitin-triggered immunity in *PxLPMO1*-silenced melon cotyledons [64]. *P. xanthii* chitin deacetylase, PxCDA, can convert chitin to chitosan to avoid recognition [69]. Martínez-

Cruz et al. [70] identified a family of conserved, secreted *P. xanthii* chitinases, known as effectors with chitinase activity (PxEWCA), which were released at pathogen penetration sites to break down immunogenic chitin oligomers, thus preventing the activation of chitin-triggered immunity. Martínez-Cruz et al. [71] identified a *P. xanthii* chitin-binding effector, PxCHBE, which can bind to chitin oligomers, preventing the activation of chitin signaling.

Another strategy used by *P. xanthii* effectors is to suppress the host-generated oxidative burst. Martínez-Cruz et al. [63] identified over 50 *P. xanthii*, known as *P. xanthii* effector candidates (PECs). *Agrobacterium tumefaciens*-mediated host-induced gene silencing assay revealed that six PECs (PEC007, PEC009, PEC019, PEC032, PEC034, and PEC054) are required for *P. xanthii* pathogenesis. The mutants *pec007*, *pec009*, *pec019*, *pec032*, *pec034*, and *pec054* showed reduced fungal growth and increased production of the reactive oxygen species H₂O₂ in the epidermal cells of melon cotyledons [63]. Three effectors (PEC019, PEC032, and PEC054) were confirmed to be phospholipid-binding protein, α -mannosidase, and cellulose-binding protein by an in vitro expression assay on *Escherichia coli* [63]. The putative novel targets for these fungal effectors are predicted to be host-cell plasma membrane, host-cell glycosylation, and the cellulose-triggered immunity [63]. Li et al. [19] identified six CSEPs from *P. xanthii*, which potentially induced cell death in cucumber, as well as the host targets of these fungal effectors using the yeast two-hybrid (Y2H) assay. Previous studies indicated that host cell death can be classified as either disease resistance or susceptibility [73,74]. The hypersensitive response (HR) correlated with the effector-triggered immunity (ETI) is a well-studied cell death response in plants [75]. The plant STAY-GREEN (SGR) genes, which encodes chloroplast proteins, can serve as regulators of Chl degradation [76], and it is also involved in pathogenic processes in plants [19]. In the cucumber genotype Gy14, the recessive gene *Cssgr* (Q108R) from a single amino acid substitution, exhibited long-term resistance to multiple pathogens [77,78]. Three CSEP effectors (CSEP30, CSEP47, and CSEP48) interacted with both *CsSGR* and *Cssgr*, but only the mature form of CSEP30 (CSEP30S^{ASP}) specifically interacted with *Cssgr*, and not with *CsSGR* [19]. *P. xanthii* infection of the moderately powdery mildew-resistant cucumber genotype Gy14 induced necrotic lesions and specific expression of *Cssgr*, together with defense response-related genes (*CsPR1* and *CsLecRK6.1*). The authors suggested that the interaction between *Cssgr* and CSEP30^{ASP} could trigger cell death and defense response in disease resistance in Gy14 cucumber [19].

3.2. Host–Pathogen Molecular Interactions

The biotrophic powdery mildew fungal pathogen relies on interactions with living host cells to facilitate their propagation, and the expression of several host genes, such as so-called “disease susceptibility” genes (S-gene), is essential for a successful infection [79].

First discovered in barley, the *Mildew Resistance Locus O* (MLO)-encoding plasma membrane-anchored protein, is a family of known S-genes associated with powdery mildew susceptibility in plants [80,81]. In dicot species, all known MLO-like susceptibility genes for powdery mildew are phylogenetically clustered in clade V. Among the 16 *CsMLO* genes identified in cucumber, the clade V *CsMLO1*, *CsMLO8*, and *CsMLO11* genes are correlated with powdery mildew susceptibility [82–87]. They may promote powdery mildew susceptibility by modulating ROS [83,84], phenylpropanoid biosynthesis pathway [83], calcium signaling [84,85], or ubiquitin pathway [86].

A previous study demonstrated a transposable element (TE) insertion in the susceptibility gene *CsMLO8*, resulting in hypocotyl resistance to powdery mildew in cucumber [82]. Insertion of a non-autonomous Class LTR retrotransposable element in the resistant genotype caused aberrant splicing of *CsMLO8* mRNA, with 72 or 174 bp transcript deletions [82]. Inoculation of a susceptible cucumber genotype with the powdery mildew pathogen *P.*

xanthii induced transcriptional upregulation of *CsMLO8* in hypocotyl tissue, but not in cotyledon or leaf tissue. Heterologous expression of the wild-type allele of *CsMLO8*, cloned from the susceptible cucumber genotype, in a tomato *mlo*-mutant restored powdery mildew susceptibility; while heterologous expression of the *CsMLO8* allele cloned from the resistant cucumber genotype failed to restore susceptibility [82]. The authors concluded that *CsMLO8* is a functional susceptibility gene to powdery mildew with transcriptional upregulation upon inoculation with *P. xanthii*, while the loss-of-function-resistant mutant TE-allele of *CsMLO8* can be found in 31 out of 115 resequenced cucumber accessions using in silico analysis [82].

Later, Berg et al. [87] found that overexpression of the cucumber *CsMLO1* or *CsMLO8* in the tomato *mlo*-mutant completely restored susceptibility to powdery mildew, while overexpression of *CsMLO11* only partially restored susceptibility. In a recent study, Dong et al. [88] demonstrated that *CsMLO8/11* are required for the complete susceptibility of cucumber stem to powdery mildew. Knockout mutants *CsMLO8* and *CsMLO11* generated by CRISPR/Cas9 showed improved resistance to powdery mildew, increased accumulation of ROS in stem, and upregulated defense-related genes. Several components are involved in ROS-related plant defense responses. NADPH oxidase/respiratory burst oxidase homolog (Rboh) proteins function in localized ROS bursts [89]. CYSTEINE-RICH RECEPTOR-LIKE PROTEIN KINASE 2 (CRK2) interacts with RbohD for the elicitor-induced ROS burst [90]. Using a protein interaction assay, Dong et al. [84] demonstrated that *CsMLO8* and *CsMLO11* could physically interact with *CsRbohD* and *CsCRK2*, respectively. *CsMLO8* and *CsCRK2* showed competitive interaction with the C-terminus of *CsRbohD* to affect *CsCRK2*-*CsRbohD* module-mediated ROS production during defense against powdery mildew [84].

Sun et al. [83] demonstrated that a reverse mutation of *CsMLO8* results in susceptibility to powdery mildew via inhibiting cell wall apposition formation and cell death in cucumber. A powdery mildew-susceptible mutant, m6326, deriving from the EMS-mutagenized population of a natural *mlo*-mutant line No. 26 (powdery mildew resistant), was identified as a *CsMLO8* revertant [83]. In the susceptible m6326, higher rate of spore penetration, longer hypha, and more conidia were observed than that in the resistant No. 26. In the resistant line No. 26, the phenylpropanoid biosynthesis pathway and ROS scavenging genes were significantly upregulated compared with that in susceptible line m6326 [83].

Recent studies highlighted the importance of calcium signaling in MLO-mediated powdery mildew susceptibility, in which MLO proteins may act as Ca^{2+} -influx channels [84,85]. Transcriptome and proteome data revealed enriched Ca^{2+} signal decoding genes and proteins during cucumber interaction with the powdery mildew pathogen *P. xanthii*, e.g., the upregulated gene encoding the kinesin-like calmodulin-binding protein (KCBP)-interacting Ca^{2+} -binding protein (*CsKIC*) and the upregulated proteins calmodulin-like protein 28 (*CsCML28*), and Ca^{2+} -dependent protein kinase 11 (*CsCPK11*) [85]. Using the yeast two-hybrid analysis and the firefly luciferase complementation imaging (LCI) test, Ma et al. [85] identified that *CsKIC* can interact directly with the C-terminus of the clade V cucumber *CsMLOs*, *CsMLO8*, *CsMLO1*, and *CsMLO11* [85]. CRISPR/Cas9-mediated multiplex gene editing in a powdery mildew-susceptible cucumber genotype CG9199 revealed that the silencing of *CsKIC*, as well as co-silencing *CsKIC* with *CsMLO8*, resulted in enhanced resistance, suggesting that *CsKIC* and *CsMLO8* act as positive regulators of powdery mildew susceptibility in cucumber [85]. However, co-silencing *CsKIC* with both *CsMLO1* and *CsMLO8* simultaneously resulted in a significantly more resistant phenotype compared with silencing *CsKIC* alone or the simultaneous silencing of both *CsMLO1* and *CsMLO8* [85]. The authors concluded that *CsKIC* collaborates with the clade V cucumber *CsMLOs* to promote powdery mildew invasion [85]. On the other hand, gene editing in a powdery

mildew-resistant cucumber genotype CG0003 revealed that silencing of *CsCML28* and *CsCPK11* resulted in increased susceptibility to powdery mildew, suggesting that *CsCML28* and *CsCPK11* act as negative regulators in promoting powdery mildew susceptibility in cucumber [85].

Analysis of the structure of 414 putative promoter regions of melon *CmMLO* genes revealed that TC box-like and thymine-rich motifs are overrepresented in the putative promoter regions of the clade V *CmMLO* susceptible genes upregulated upon powdery mildew infection [91]. A melon clade V *CmMLO* gene enriched for these motifs was strongly upregulated following challenge with the powdery mildew pathogen *P. xanthii* [91]). Zhang et al. [92] identified the melon *CmMLO5* gene as playing a negative role in regulating powdery mildew resistance in the susceptible melon line (Topmark). A single-nucleotide substitution (C to T) at 572 bp, causing a change in amino acid from T to I, resulted in a loss-of-function mutant, thus conferring powdery mildew resistance in melon [92]. The melon Dominant Suppressor of KAR2 (*CmDSK2b*), a ubiquitin receptor protein, showed a positive regulation of powdery mildew susceptibility in melon through interactions with melon *CmMLO5* [86]. Yeast two-hybrid screening, luciferase complementation assay (LCA), and bimolecular fluorescence complementation (BiFC) assay identified *CmDSK2b* as the binding partner of *CmMLO5* [86]. Transcriptional expression of the *CmDSK2b* is induced by *P. xanthi* infection, which is positively related to the disease susceptibility in melon. The authors demonstrated that *CmDSK2b* contributes to fungal susceptibility by promoting ubiquitin-mediated proteasomal degradation of the *CmMLO5* protein, based on a transient co-expression assay in *Nicotiana benthamiana* [86].

Many recent studies identified other negative modulators of powdery mildew resistance in cucurbits, functioning through the regulation of ROS and hypersensitive response-associated genes [6,18,93–95], ABA signaling pathway-associated genes, and target of rapamycin (TOR) signaling pathway-associated genes [96–98], or ethylene biosynthesis-associated genes [99].

A leucine-rich repeat-only gene *CsLRR1* has been shown to modulate powdery mildew susceptibility in cucumber. Xu et al. [93] identified two alleles of the cucumber gene *CsLRR1*, which encodes a protein with eight leucine-rich repeat (LRR) motifs. A single-nucleotide substitution in the sequence encoding the third LRR motif of the *CsLRR1* resulted in substitution of the amino acid threonine (Thr171, ACT), i.e., allele *CsLRR1^C*, in the powdery mildew-resistant cucumber genotype SSSL508-28 in place of the amino acid asparagine (Asp171, AAT), i.e., allele *CsLRR1^A*, in the susceptible genotype D8 [93]. Overexpression of the allele *CsLRR1^C* in the susceptible genotype D8 increased powdery mildew resistance, and the silencing of *CsLRR1^C* in the resistant line via CRISPR/Cas9 editing promoted powdery mildew susceptibility, while overexpression of the allele *CsLRR1^A* in the susceptible D8 did not change the susceptibility of D8. The authors concluded that the *CsLRR1^C* allele is negatively associated with disease symptoms and confers powdery mildew resistance in cucumber. They also concluded that the non-synonymous mutation in the third LRR motif of *CsLRR1*, resulting in the *CsLRR1^A* allele, appears to account for the altered gene function [93]. The authors inferred that in *CsLRR1^C*, an extra hydrogen bond forms between the 171st amino acid and the 146th amino acid, which is likely to be the source of functional variation between *CsLRR1^A* and *CsLRR1^C* [93]. Yeast one-hybrid assay verified that the cucumber *CsbZIP63*, a salicylic acid-responsive bZIP transcription factor, can bind directly to the ACGT-box motif in the *CsLRR1* promoter to initiate its expression, while silencing of *CsbZIP63* led to powdery mildew susceptibility in the resistant plant genotype [93]. Moreover, ROS levels were significantly higher in resistant SSSL508-28 than in susceptible D8 during the first 48 h post-powdery mildew infection [18]. Hypersensitive-response-associated and ROS-detoxification-associated genes were differentially upregulated post-infection

in SSSL508-28 [6, 93]. In another study, Liu et al. [94] demonstrated that the cucumber *CsbZIP90* gene, which encodes a basic leucine zipper (bZIP) transcription factor, suppresses cucumber resistance to *P. xanthii* resistance by modulating ROS. Transient overexpression of *CsbZIP90* in cucumber cotyledons decreased resistance to *P. xanthii*, while silencing of *CsbZIP90* increased resistance to *P. xanthii*. *CsbZIP90* negatively regulates the expression of ROS-related genes and the activities of ROS-related kinases [94]. Map-based cloning revealed that the mutation in a highly conserved amino acid of the cucumber porphobilinogen deaminase (*CsPBGD*) leads to enhanced resistance to powdery mildew, alongside increased H_2O_2 accumulation [95].

Meng et al. [96] identified two translationally controlled tumor protein (*CsTCTP*) genes, *CsTCTP1* and *CsTCTP2*, acting as negative modulators in cucumber resistance to defense response to powdery mildew pathogen *P. xanthii*. Transient overexpression of either *CsTCTP1* or *CsTCTP2* in cucumber cotyledons impaired resistance to *P. xanthii*, whereas silencing of either *CsTCTP1* or *CsTCTP2* enhanced cucumber resistance to *P. xanthii*. *CsTCTP1* has shown to participate in the defense response to *P. xanthii* by regulating the expression of certain defense-associated genes and/or abscisic acid (ABA) signaling pathway-associated genes, and *CsTCTP2* participates through regulating the expression of target of rapamycin (TOR) signaling pathway-associated genes. In another study, Chen et al. [97] demonstrated that cucumber *CsTCTP* interacts with a small GTPase, *CsRab11A*, and promotes the activation of TOR in response to powdery mildew pathogen *P. xanthii*. The role of TOR in plant disease resistance depends on its regulatory activity. The regulation function of TOR in response to *P. xanthii* by the upstream regulators, *CsTCTP* and *CsRab11A*, are sophisticated [97]. Pretreatment of cucumber plants with a TOR inhibitor enhances plant resistance to *P. xanthii* [97,98], while pretreatment with a TOR activator increases plant susceptibility [97]. Upon *P. xanthii* attack, inhibition of cucumber TOR mobilized unique molecular players associated with cell wall modification, redox state, ABA signaling, gene transcription regulation, and respiratory burst, and enhanced the expression of basic Helix–Loop–Helix 35 (*bHLH35*) and FCS-Like Zinc finger 15 (*FLZ15*) genes [98]. Silencing of *bHLH35/FLZ15* decreased cucumber resistance to *P. xanthii*. The gene *FLZ15*, encoding FCS-Like Zinc finger 15, and the gene *bHLH35*, encoding the transcription factor basic Helix–Loop–Helix 35, were identified as potential downstream genes of TOR in the response to *P. xanthii* infection based on quantitative reverse transcription-PCR and virus-induced gene silencing assays [98].

Wu et al. [99] demonstrated that the melon ethylene response factor *CmRAP2-13* negatively regulates red light-induced resistance of melon to powdery mildew by inhibiting ethylene biosynthesis. *CmRAP2-13* can inhibit the expression of key ethylene synthesis genes *CmACS10* and *CmERF27* by binding to GCC-box in the promoters. The protein-level interaction between *CmRAP2-13* and *CmERF27* indicated that the presence of *CmRAP2-13* can weaken the transcriptional activation of *CmERF27* on *CmACS10* [99].

4. Plant Defense Responses Against Powdery Mildew

4.1. Recognition of Powdery Mildew Pathogens

4.1.1. PRRs (Pattern Recognition Receptors) and R Proteins

Powdery mildew constitutes one of the major phytopathological threats to cucumber (*C. sativus*) cultivation, leading to substantial yield losses. The most effective strategy for its control remains the breeding of pathogen-resistant cultivars. A key component of effective plant immunity is the early recognition of the pathogen, which triggers a cascade of defense signaling.

Plants, including cucumbers, utilize two primary types of immune receptors: pattern recognition receptors (PRRs) and intracellular resistance proteins (R proteins). PRRs,

localized in the plasma membrane, are responsible for detecting pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), the latter originating from host cells and released in response to infection or physical damage [100]. Recognition of these signals activates PAMP-triggered immunity (PTI), providing a basal level of protection (Figure 3).

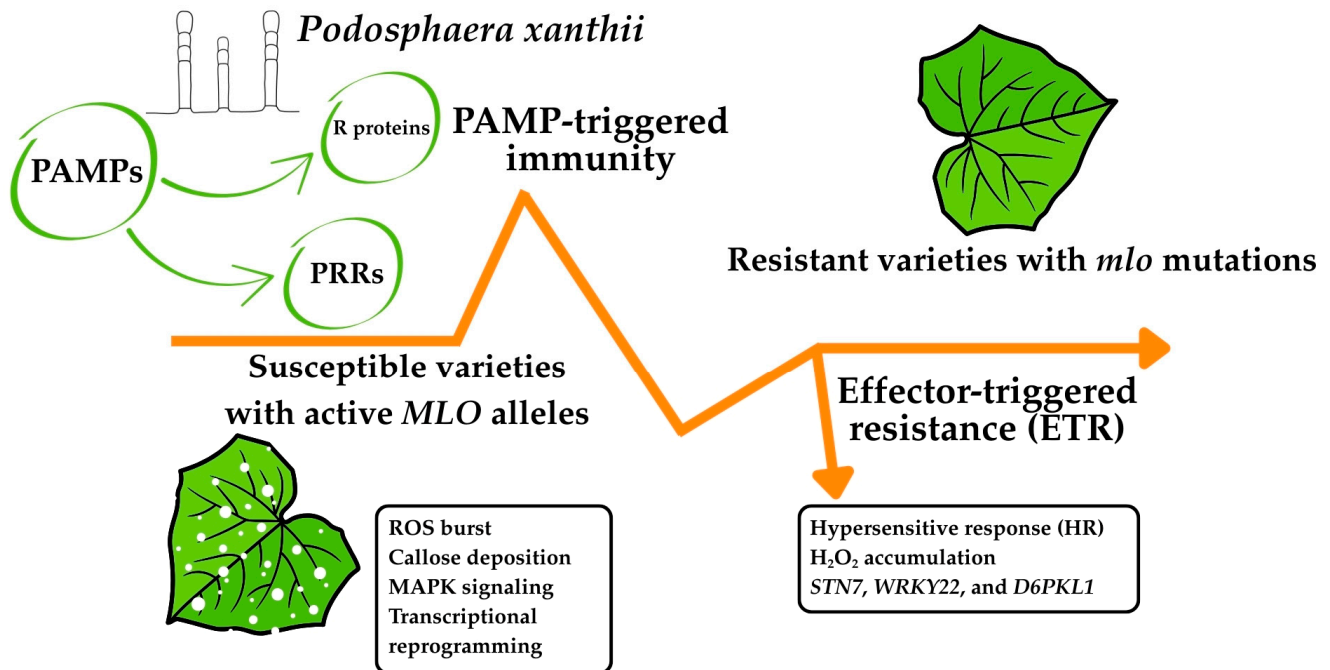


Figure 3. Schematic model of the immune response in cucurbits against *Podosphaera xanthii*. Recognition of PAMPs by PRRs triggers PTI, leading to ROS burst, callose deposition, and defense gene activation. In susceptible varieties with functional *MLO* alleles, effectors suppress PTI, enabling infection. In resistant varieties with *MLO* mutations or R gene recognition, ETR activates stronger defenses, including HR, H₂O₂ accumulation, and expression of defense-related genes.

Receptor-like kinases (RLKs) play a pivotal role among PRRs, comprising a large family of membrane proteins involved in the response to pathogen. In cucumber, genes belonging to the *CsCRK* (cysteine-rich RLK) family have been implicated in immune responses. Comparative studies have shown that infection in a resistant cucumber cultivar leads to increased expression of *CsCRK* genes, whereas their expression is reduced in susceptible lines [101]. Transcriptomic analysis of two contrasting cultivars—the resistant SSL508-28 and the susceptible D8—at two days post-inoculation (dpi) with powdery mildew revealed that many *CsCRK* genes participate in the defense response. Significantly lower expression is observed in the susceptible D8 cultivar compared to the control. Another example of a PRR is the lectin receptor kinase *CsLecRK6.1*, which recognizes PAMPs and initiates downstream defense responses [102]. Kim and Kang [102] demonstrated that β -aminobutyric acid (BABA) induces cucumber resistance to powdery mildew by activating immune-related genes. Most of these genes peaked in expression 48 h after BABA application, whereas *CsLecRK6.1* reached its highest expression level at 24 h post-treatment. In contrast, intracellular R proteins detect specific pathogen effectors delivered into the host cytoplasm. The interaction between the effector and the R protein, as described by the gene-for-gene model, triggers effector-triggered immunity (ETI), characterized by a stronger and more specific immune response.

Sixteen members of the *CsMLO* gene family have been identified in the cucumber genome, among which three—*CsMLO1*, *CsMLO8*, and *CsMLO11*—belong to clade V and have been associated with susceptibility to powdery mildew [83]. *CsMLO8* co-localizes

with a major-effect recessive QTL on chromosome 5, conferring resistance in leaves and the hypocotyl [2,5]. *CsMLO1* and *CsMLO11* are associated with QTLs pm1.1 and pm6.1, respectively. Loss-of-function mutations in *CsMLO1* result in enhanced resistance by eliminating a susceptibility factor. Additionally, *CsMLO8* and *CsMLO11* interact with ROS-producing proteins such as *CsRbohD*. Disruption of these genes abolishes the interaction, leading to increased resistance [84]. Transcription factors such as *WRKY22* and the *STN7* receptor also play a crucial role in the early stages of signal transduction in response to infection. *WRKY22* has been identified as a component of plant–pathogen interaction pathways in the KEGG database [103]. In the resistant cultivar ‘Meltem’, *WRKY22* expression increased at 1 dpi and then declined, whereas no expression was observed in the susceptible cultivar ‘Camlica’, suggesting that *WRKY22* is involved in regulating early immune signaling against *P. xanthii* [104].

4.1.2. Downstream Signaling Pathways (SA, JA, and ROS Bursts)

In response to powdery mildew (PM) infection, cucumber plants initiate a complex network of signaling cascades that orchestrate the immune response. The three major signaling components involved are salicylic acid (SA), jasmonic acid (JA), and reactive oxygen species (ROS). Synergistic and antagonistic interactions among these pathways determine the effectiveness of the plant’s defense against biotrophic pathogens such as *P. xanthii*. Salicylic acid plays a central role in the induction of systemic acquired resistance (SAR), which is particularly important in combating biotrophic pathogens. Activation of the SA pathway upregulates pathogenesis-related (PR) genes, including *CsPR1* and *CsPR3*, encoding hydrolases such as β -1,3-glucanases and chitinases that degrade fungal cell walls [102,105].

The exogenous application of β -aminobutyric acid (BABA) increases endogenous SA levels by 3.8-fold and enhances the expression of SAR-related genes. BABA also increases the activity of phenylalanine ammonia-lyase (PAL), which is a key enzyme in SA and lignin biosynthesis. Lignification of cell walls serves as a physical barrier that hinders pathogen penetration [106].

ROS, particularly hydrogen peroxide (H_2O_2), are rapidly synthesized at infection sites and act as both signaling molecules and cytotoxic agents. In cucumber, their production is mainly regulated by NADPH oxidases, particularly *CsRbohD*, which form complexes with susceptibility proteins *CsMLO8* and *CsMLO11*. Loss-of-function mutants for these MLO genes exhibit up to 68% higher H_2O_2 accumulation in stems and significantly enhanced resistance to PM, indicating a negative regulatory role of MLO proteins in immunity [84].

Ethylene (ET) functions as a precursor of the ROS burst. The early activation of ethylene biosynthesis genes, such as *CsACS1* and *CsACS1-2*, results in increased expression of *CsRbohD* and H_2O_2 accumulation. This leads to growth inhibition of the fungal pathogen via activation of the hypersensitive response (HR) and localized cell death [107]. Exogenous ET application further amplifies oxidative stress and delays chlorophyll degradation, correlating with reduced disease severity.

Although JA signaling is traditionally associated with resistance against necrotrophic pathogens and herbivorous insects, its role in PM defense is increasingly recognized [108,109]. PM infection significantly upregulates expression of *LOX1* and *LOX23*, encoding lipoxygenase enzymes involved in JA biosynthesis—up to a 4.5-fold increase compared to control plants [102,110].

JA also promotes the biosynthesis of secondary metabolites, such as flavonoids (e.g., apigenin), with strong antifungal activity [111]. Application of a phenolic-rich CFRE extract can reduce PM development by up to 97%, confirming the efficacy of JA-mediated defense mechanisms.

4.1.3. Crosstalk and Integration of SA, JA, and ROS Pathways

The SA, JA, and ROS signaling pathways function as an integrated regulatory system of plant immunity [112]. SA often acts synergistically with ROS, especially in the context of HR induction and localized cell death, while SA–JA interactions are frequently antagonistic [108,113,114]. Nevertheless, precise and coordinated regulation of these pathways is essential for mounting an effective and balanced defense against diverse pathogens. Additionally, infection induces increased activity of antioxidant enzymes such as peroxidase (POD) and superoxide dismutase (SOD), which mitigate oxidative damage by modulating ROS levels, while preserving their signaling function [114].

4.1.4. Pathogen Strategies to Maintain Host Cell Viability and Later Stages of Pathogenesis

As an obligate biotroph, *P. xanthii*—the causal agent of powdery mildew in cucurbits—relies on maintaining the viability of host epidermal cells throughout much of its infection cycle. To preserve the living environment necessary for nutrient uptake via haustoria, the pathogen deploys a suite of molecular strategies to manipulate host immunity and suppress premature cell death.

A central mechanism involves the secretion of over 50 *P. xanthii*-encoded effector proteins (PECs) that interfere with early defense signaling [63]. Several of these effectors, including PEC009, PEC019, PEC032, PEC034, and PEC054, have been shown to suppress PAMP-triggered immunity (PTI) and inhibit the host reactive oxygen species (ROS) burst [63]. Their silencing results in increased H₂O₂ accumulation and reduced fungal colonization, underscoring their essential role in dampening ROS-mediated responses that would otherwise lead to hypersensitive response (HR) and host cell death [115]. These effectors also target host plasma membrane integrity, cell wall metabolism, and glycosylation processes to blunt early immune activation. By inhibiting ROS production and downstream HR, *P. xanthii* ensures sustained host cell viability during the early biotrophic phase. This is crucial for the formation and function of haustoria—specialized feeding structures that extract nutrients without causing lysis of host cells [63,64]. Simultaneously, the pathogen limits the expression of damage-associated molecular patterns (DAMPs), thereby avoiding robust immune responses that would disrupt its lifecycle. While host cell preservation is a hallmark of early infection, localized host cell death may occur at later stages [116]. This may be due to the activation of salicylic acid (SA)-dependent pathways, environmental stressors (e.g., senescence, end of growing season), or as part of the pathogen's lifecycle strategy—possibly facilitating fungal sporulation or sexual reproduction (e.g., cleistothecia formation). In some cases, this cell death can also be viewed as a host resistance mechanism that restricts further fungal spread.

4.2. Natural and Engineered Resistance Mechanisms

Cucurbit plants, including cucumbers (*Cucumis sativus*), employ both natural genetic resistance mechanisms and biotechnological strategies based on genome editing to combat infections caused by powdery mildew. Intensive genetic and functional research in recent years has led to the identification of key resistance loci and susceptibility genes. Targeted modification of these enables the development of durable and stable resistance. Genome-wide association studies (GWASs) have facilitated the identification of numerous quantitative trait loci (QTLs) associated with resistance to powdery mildew in cucumber. To date, thirteen major resistance loci have been identified: *pmG1.1*, *pmG1.2*, *pmG2.1*, *pmG2.2*, *pmG3.1*, *pmG4.1*, *pmG4.2*, *pmG5.1*, *pmG5.2*, *pmG5.3*, *pmG5.4*, *pmG6.1*, and *pmG6.2*, distributed across most chromosomes except chromosome 7. Among them, *pmG2.1*, *pmG3.1*, and *pmG4.1* are novel discoveries, while the others overlap with previously identified QTLs [117]. Within these loci, candidate genes have been located that are orthologous to

well-known susceptibility (S) genes, for example, *PMR5*, *PMR6*, and *MLO* have been located. These genes play critical roles in fungal infection by members of the order *Erysiphales*. One of the best characterized susceptibility genes in cucumber is *CsMLO1*, where loss-of-function mutations confer durable and stable resistance to powdery mildew. The *pm5.1* locus corresponds directly to *CsMLO1*, and its deletion is necessary—though not sufficient—for full resistance, suggesting a polygenic nature of the trait [118].

Cucumber cultivars that are naturally resistant exhibit increased expression of defense-related genes such as *STN7*, *WRKY22*, and *D6PKL1*. These genes are involved in cell wall reinforcement, hypersensitive response (HR), and the production of reactive oxygen species (ROS), all of which are integral components of defense against the pathogen. The *MLO* gene family encodes proteins that facilitate pathogen development by allowing penetration of epidermal cells. Thus, *MLO* genes are ideal targets for genome editing aimed at enhancing resistance. Using CRISPR/Cas9 technology, cucumber lines have been generated with knockouts in three susceptibility genes: *CsMLO1*, *CsMLO8*, and *CsMLO11*. A triple mutant (*csml01/8/11*) shows complete resistance to powdery mildew, demonstrating an additive effect of simultaneous deactivation of multiple susceptibility loci [85].

CRISPR/Cas9-mediated mutagenesis of *CsMLO8* has yielded transgene-free resistant lines that exhibit high resistance under semi-commercial conditions, even as a single-gene knockout. Deletions in this gene result in loss of function, making this approach particularly attractive for practical breeding applications [119].

Functional studies have revealed that *CsMLO8* participates in a complex calcium signaling network. The protein interacts with components of the Ca^{2+} -dependent signaling cascade, including a kinesin-like calmodulin-binding protein (*CsKIC*), a calmodulin-like protein 28 (*CsCML28*), and a calcium-dependent protein kinase (*CsCPK11*). Silencing of these genes increases susceptibility to powdery mildew, whereas their overexpression, particularly that of *CsCPK11*, significantly enhances resistance. This indicates a positive regulatory role of calcium signaling in the immune response of cucumber [85].

Cucumber resistance to powdery mildew is governed by complex genetic mechanisms involving both naturally occurring resistance loci and susceptibility genes amenable to genome editing. Table 2 provides a summary of the susceptibility and resistance genes identified to date in cucumber. The identification and functional characterization of genes such as *CsMLO1* and *CsMLO8*, along with the application of CRISPR/Cas9 technology, open new avenues for rapid and precise improvement of cucumber cultivars toward durable powdery mildew resistance. Integration of these strategies with molecular insights—particularly into Ca^{2+} -dependent signaling pathways—could greatly accelerate the development of modern breeding programs under changing environmental conditions and increasing pathogen pressure.

Table 2. Powdery mildew resistance and susceptibility genes identified in cucurbits.

Gene Type	Gene/Locus	Species	Function/Mechanism	Reference
Susceptibility gene	<i>CsaMLO8</i>	<i>Cucumis sativus</i> (cucumber)	MLO-like gene; loss of function confers PM resistance	[119]
Susceptibility gene	<i>CsMLO1</i> , <i>CsMLO11</i>	<i>Cucumis sativus</i>	Other MLO family members interacting with <i>CsaMLO8</i>	[85]
Resistance gene	<i>Csa5G623470</i> (MLO-like)	<i>Cucumis sativus</i>	Candidate gene within <i>pm-s</i> locus; associated with PM resistance	[5]
Resistance gene	<i>CsCPK11</i>	<i>Cucumis sativus</i>	Calcium-dependent protein kinase; positive regulator of resistance	[85]
Resistance gene	<i>CRK</i> (<i>Pm1.1</i>)	<i>Cucumis sativus</i>	Cysteine-rich receptor-like kinase; dominantly inherited PM resistance gene	[4]
Regulatory genes	<i>STN7</i> , <i>WRKY22</i> , <i>D6PKL1</i>	<i>Cucumis sativus</i>	Regulators of ROS production and hypersensitive response (HR)	[104]
Major QTLs	<i>Pm5.1</i> , <i>Pm5.2</i>	<i>Cucumis sativus</i>	Major loci linked to phosphate transporter gene <i>CsGy5G015960</i> ; confer durable resistance	[9]
Organ-specific QTLs	Chr. 1, 2, 5, 6	<i>Cucumis sativus</i>	Organ-specific expression patterns of PM resistance	[1]

5. Breeding and Biotechnological Strategies for Resistance

5.1. Conventional Breeding Approaches

Wild relatives of cultivated cucurbit crops, including primitive landraces and polyploid species, represent invaluable reservoirs of durable resistance alleles against powdery mildew (PM), caused primarily by *Podosphaera xanthii*. These wild gene pools harbor novel and broad-spectrum resistance traits that are often absent in domesticated varieties, offering a critical advantage in the face of rapidly evolving pathogen populations.

Wide hybridization techniques—crossing cultivated cucurbits with distantly related wild species such as *Cucurbita okeechobeensis* subsp. *martinezii* and *C. lundelliana*—have enabled the transfer of resistance alleles into elite cultivars [120]. However, these crosses are frequently hampered by pre- and post-zygotic barriers, leading to embryo abortion or hybrid sterility. To overcome these limitations, embryo rescue has been employed as a key tissue culture strategy, allowing immature hybrid embryos to develop on artificial media and yield viable offspring [121]. This approach has been instrumental in the successful introgression of resistance traits into cucumber, melon, squash, and pumpkin, and also supports polyploidization and germplasm rejuvenation [121].

Introgression breeding, complemented by chromosome engineering, allows for the stable incorporation of specific resistance loci into cultivated genomes. Notable examples include the integration of the Pm-0 resistance gene—originally from wild *C. okeechobeensis*—into *C. pepo* and *C. moschata*, now widely used in commercial cultivars [122]. Similarly, in cucumber, accessions such as CS-PMR1 have been effectively used to develop resistant varieties like ‘Kyuri Chukanbohon Nou 5 Go’, providing robust and stable resistance under field conditions [123].

Quantitative trait loci (QTLs) such as Pm5.1 and Pm5.2, located on chromosome 5 and associated with the phosphate transporter gene CsGy5G015960, have been identified through genome-wide association studies (GWASs) as major contributors to environmentally stable PM resistance [9,124]. These loci enhance defense by regulating hydrogen peroxide (H₂O₂) accumulation and activating class III peroxidase enzymes [9]. The polygenic and quantitative nature of PM resistance, typically inherited through additive effects, underscores the importance of pyramiding diverse resistance loci—especially those effective under different thermal regimes (e.g., 20–25 °C) [1,124].

Wild cucurbit species, particularly polyploid forms, further enhance resistance breeding due to their heterozygosity and gene dosage effects, often harboring multiple resistance alleles [125]. Chromosome engineering enables the precise selection and transfer of desired chromosome segments while minimizing linkage drag, the co-introduction of undesirable traits. Marker-assisted selection (MAS), using sequence-tagged site (STS) markers, enhances the efficiency and accuracy of these breeding strategies [121].

At the molecular level, resistance conferred by wild-derived alleles involves multiple defense pathways, including cell wall reinforcement, hypersensitive response (HR), and the production of reactive oxygen species (ROS). Key regulatory genes such as STN7, WRKY22, and D6PKL1 mediate these responses, contributing to a robust defense architecture [104].

Altogether, the strategic exploitation of wild relatives, polyploid species, and modern genomic tools significantly broadens the cucurbit resistance gene pool. These approaches offer durable, broad-spectrum, and environmentally resilient resistance to powdery mildew, thereby strengthening sustainable cucurbit crop production.

5.2. Genomics-Assisted Breeding and Gene Editing

Recent advances in genome-assisted breeding, driven by the completion of high-quality reference genome assemblies at the chromosome level—and even telomere-to-telomere (T2T) sequencing—for major cucurbit species, have significantly accelerated the discovery, precise cloning, and functional characterization of resistance loci to PM in cultivated Cucurbitaceae.

Currently, over 18 key cucurbit species, including cucumber (*Cucumis sativus*), melon (*C. melo*), watermelon (*Citrullus lanatus*), and squash (*Cucurbita pepo*, *C. moschata*, *C. maxima*), possess high-quality, chromosome-scale reference genomes [126,127]. These reference genomes have enabled comparative and evolutionary analyses of resistance gene regions across cucurbit species. Conserved patterns of synteny and genome rearrangements among species have facilitated the transfer and mapping of resistance genes, while also enhancing annotation accuracy.

Chromosome-scale genomic data, combined with genome-wide association studies (GWASs) and high-density genetic maps, have enabled the precise mapping and cloning of Pm resistance genes and QTLs. In cucumber, at least 19 consensus resistance QTLs have been identified, while in *C. moschata* (butternut squash), genomic and transcriptomic analyses have revealed candidate genes and SNPs located within resistance gene clusters [3,9]. Key resources such as the Cucurbit Genomics Database (CuGenDB) centralize these genomic datasets, providing breeders and researchers with access to high-quality genomes and trait-associated information.

Marker-assisted selection (MAS) allows for the rapid and precise introgression of resistance alleles. The pm-s locus, mapped to a 135.7 kb region on chromosome 5, contains 21 candidate genes, including Csa5G623470, which encodes an MLO-like protein and is considered the most likely resistance gene. Tightly linked SSR markers (pmSSR27 and pmSSR17), located at distances of 0.1 and 0.7 cM, respectively, enable high-resolution MAS [5].

Numerous QTLs conferring PM resistance have been mapped to chromosomes 1, 2, 5, and 6. A key locus, pm5.1, accounts for over 30% of phenotypic variance and was identified using SSR, SNP, and SLAF markers in F₂ populations and recombinant inbred lines (RILs). Some QTLs exhibit organ-specific expression, emphasizing the need to pyramid multiple loci to achieve durable, broad-spectrum resistance [1].

Gene editing strategies, particularly using the CRISPR/Cas9 system, have revolutionized both functional analyses and practical breeding for resistance. The MLO gene family, which encodes susceptibility factors facilitating fungal penetration, has become a prime target. Knockout of CsMLO8 in susceptible cucumber varieties produced transgene-free mutants (Csamlo-cr-1, Csamlo-cr-2) that displayed high levels of resistance under semi-commercial conditions [119].

Using multiplex gene editing to target CsMLO1, CsMLO8, and CsMLO11 led to the development of triple mutants with complete resistance to PM. Transcriptomic and proteomic analyses revealed that CsMLO8 physically interacts with calcium signaling regulators such as CsKIC, CsCML28, and CsCPK11, which positively modulate the resistance response. Overexpression of CsCPK11 enhanced resistance, while silencing it increased susceptibility, underscoring their critical regulatory role [85].

These precise gene editing strategies, supported by genomic insights, greatly shorten breeding cycles and enable the targeted deployment of PM resistance in elite cultivars and breeding lines, without the drawbacks of linkage drag.

5.3. Transgenic and RNAi-Based Strategies

RNA interference (RNAi) has emerged as a potential tool for suppressing essential fungal genes involved in penetration, virulence, or growth. Although direct applications in cucumber are limited, RNAi-based silencing of fungal genes holds promise for PM control [128,129].

Virus-induced gene silencing (VIGS) has been used to validate candidate resistance genes in cucumber, showing that RNAi can be used to modulate the expression of both host and pathogen genes to enhance resistance [130]. Transgenic overexpression of cucumber defense genes has been shown to significantly enhance PM resistance. A notable example is *CsGy5G015960*, a phosphate transporter gene identified via GWASs. Overexpression of its resistant haplotype (Hap. 1) in susceptible lines led to markedly reduced disease symptoms [9]. Mechanistically, *CsGy5G015960* maintains elevated hydrogen peroxide (H₂O₂) levels by downregulating multiple class III peroxidase genes, thereby intensifying the oxidative burst and hypersensitive response (HR), limiting fungal colonization. Other defense-associated genes, including pathogenesis-related proteins (β-1,3-glucanase, chitinase), transcription factors (*WRKY22*), and kinases (*STN7*, *D6PKL1*), contribute to resistance when overexpressed, facilitating cell wall reinforcement, ROS accumulation, and programmed cell death [131,132].

In summary, Table 3 presents commercial cucurbit varieties with available data on yield performance and powdery mildew resistance, along with the breeding methods used in their development. This overview serves as a practical reference for breeders and researchers aiming to develop resistant cultivars without compromising high yield potential.

Table 3. Commercial cucurbit varieties with known yield and powdery mildew resistance levels, and their breeding methods.

Crop	Variety/Line Name	Resistance Level	Breeding Method	Reference/Source
Cucumber	PI 197088-5	Highly resistant (temperature-independent resistance)	Backcross breeding for resistance genes	[133,134]
Cucumber	Natsufushinari	Resistant (at high temperature)	Pure line selection/backcross breeding	[133]
Cucumber	Jinza 1 hao, 808, SC-8	Resistant	Selection	[133]
Cucumber	R1461	Highly resistant	Seedling disease resistance screening	[135]
Cucumber	BK2	Resistant	Seedling disease resistance screening	[135]
Cucumber	9930, H136	Susceptible	Selection	[135]
Cucurbita	YD26 (<i>C. moschata</i>)	Highly resistant	Hybridization and selection	[135]
Cucurbita	SF02 (<i>C. moschata</i>)	Highly susceptible	Selection	[3]
Cucurbita	Varieties with Pm-0 locus	Resistant	Wide hybridization and introgression	[3]
Zucchini	Varieties carrying CpPM10.1	Resistant	Fine mapping, backcross breeding	[3]
Pumpkin	Commercial cultivars with Pm-0 introgression	Resistant	Wide hybridization and backcross breeding	[3]

6. Integrated Management Strategies

Managing powdery mildew in cucurbit crops is a significant challenge for farmers around the world. This destructive disease weakens plants, reduces yields, and diminishes the quality of produce intended for sale. Relying solely on fungicides has serious limitations, such as the development of resistance and regulatory pressures. To achieve lasting and effective control of the disease, a coordinated approach is crucial [136]. The comprehensive strategy of disease prevention and control combines various methods and focuses mainly on choosing resistant varieties, good cultural practices, biological control and using fungicides of various modes of action (Figure 4) [46,137].

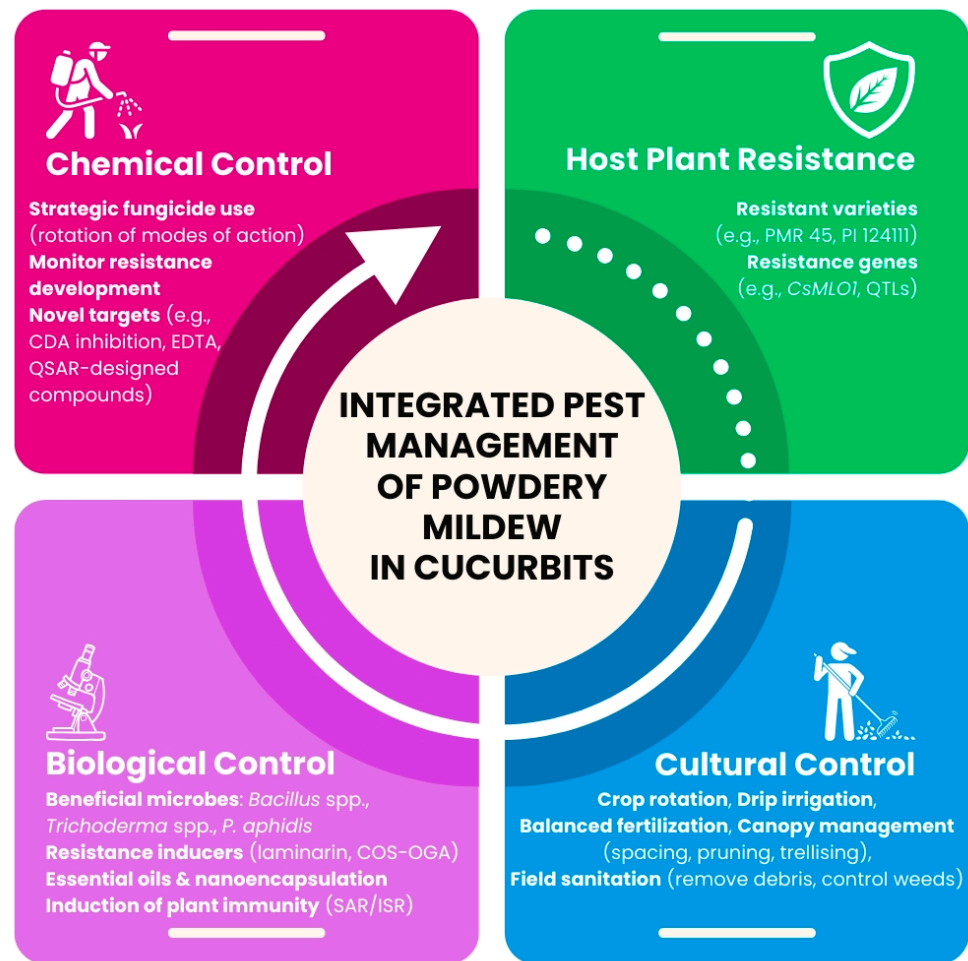


Figure 4. Integrated pest management strategies for controlling powdery mildew in cucurbits.

6.1. Host Plant Resistance

Using varieties with genetic resistance is the most sustainable control method. Resistant cucumber varieties have been developed and offer partial or complete control depending on the physiological races of the pathogen (mainly *P. xanthii*) [21,136]. However, the fungus' resistance is not always durable. Studies in Europe and the United States show that new pathogen races regularly emerge, overcoming previously effective resistance genes [21,46]. Therefore, resistance should be integrated with other elements of integrated pest management (IPM) to ensure long-term effectiveness.

Some plants, such as melon, cucumber and squash, have built-in resistance genes which offer varying levels of protection against specific types of pathogens. While complete immunity is rare, and pathogens can adapt over time, planting partially resistant plants can significantly delay the onset of an outbreak, reduce disease severity, and reduce the need for fungicides.

6.2. Cultural Control

Cultural practices aim to reduce the environmental conditions favorable for PM development. Dense planting, high nitrogen fertilization, and poor air circulation create optimal microclimates for spore germination and pathogen spread [46,47,49,51,137].

To reduce inoculum build-up, avoid planting cucurbits in the same location each season and destroy volunteer cucurbits. Furthermore, balanced plant nutrition is essential. Excessive nitrogen fertilization stimulates dense, succulent growth, which is often accompanied by weakened cell walls, thereby increasing susceptibility to infection. Ade-

quate potassium strengthens cell walls and induces defense responses, while phosphorus supports root health and stress tolerance. Although PM pathogens are airborne, rotating crops with non-cucurbit species reduces local inoculum over time. Combining rotation with sanitation—such as removing volunteer plants and weed hosts—is another effective strategy. Optimization of plant architecture and planting density enhances airflow within the canopy, thereby reducing relative humidity (RH) and accelerating leaf drying. These conditions are less conducive to spore germination and infection by PM pathogens. Key cultural practices to achieve this optimization include maintaining adequate inter-plant spacing to prevent overcrowding and facilitating air circulation. For crops such as cucumbers and melons, trellising elevates foliage off the ground, improving air movement. Additionally, selective pruning, involving the strategic removal of older, interior, or densely clustered leaves, enhances light penetration and airflow. However, excessive pruning should be avoided to prevent inducing plant stress.

Taken together, these practices alter the microenvironment of the plant, making it more difficult for pathogens to establish and develop [137–139].

Proper sanitation reduces the initial sources of infection. This means quickly removing and destroying infected crop debris after harvest, such as through deep burial or composting in a separate area from the fields, since the fungi can survive on plant material. It is also essential to control weeds within and around fields, as many common weeds, such as wild cucurbits, can serve as alternative hosts for PM pathogens. Disinfecting tools, equipment, and greenhouse structures can also help minimize the spread of pathogens [137,140,141].

Irrigation practices, such as using drip irrigation instead of overhead watering to keep foliage dry, critically influence the development of PM. Overhead irrigation (e.g., sprinklers) raises canopy humidity and washes away fungicides or biocontrol agents, creating favorable conditions for secondary infections. Drip irrigation is recommended because it delivers water directly to the root zone, keeping foliage dry and reducing humidity [142]. Irrigation timing should allow foliage to dry before nighttime humidity increases [137].

6.3. Biological Control

Biological control offers a sustainable alternative to synthetic fungicides by using naturally occurring enemies or their byproducts to manage powdery mildew. This approach involves applying beneficial microorganisms (such as specific bacteria, fungi, or yeasts) or bioactive compounds derived from them. These agents can work through competition, parasitism, antibiosis, or by inducing the plant's natural defenses [143,144].

Sarhan et al. [145] demonstrated that *Bacillus subtilis*, *Trichoderma harzianum*, and *Serratia marcescens* significantly reduced disease severity and *P. xanthii* conidial germination in a greenhouse experiment. Among them, *B. subtilis* was almost as effective as the fungicide difenoconazole in impeding disease progress and increasing cucumber yield parameters. These bioagents also stimulate plant defense mechanisms, such as increased polyphenol oxidase (PPO) and peroxidase (PO) activity and increased total phenolic content, contributing to induced systemic resistance (ISR). According to Romero et al. [146], three strains of *B. subtilis* can be used to manage powdery mildew disease on greenhouse-grown melon.

Another important group, categorized distinctly from fungicides, comprises resistance stimulators. The main active ingredients in these products are laminarin (a β -1,3-glucan, approved in Laminone, Nutivax, Plantivax, Vaxiplant SL) or COS-OGA (chitosan oligomers + oligogalacturonides in Fytosave SL). Laminarin, a β -glucan oligosaccharide elicitor derived from the brown alga *Laminaria digitata*, was successfully evaluated against grape powdery mildew (*Erysiphe necator*) on *Vitis vinifera* cv. Moscato [147]. As a natural resistance inducer, laminarin stimulates systemic acquired resistance (SAR) in grapevines,

enhancing the production of defense compounds such as salicylic acid and pathogenesis-related proteins. In field and potted trials, laminarin significantly reduced disease severity (77–94% on leaves) and incidence compared to untreated controls, demonstrating its potential for sustainable disease management. However, its efficacy was consistently lower than sulfur under high disease pressure (e.g., warm, low-humidity conditions), particularly on grape clusters [147].

COS-OGA, another elicitor made of a stabilized complex of chitooligosaccharides (COSs), derived from fungal cell walls or crustacean exoskeletons, and oligogalacturonides (OGAs), derived from plant pectin, activates salicylic acid-mediated plant defenses. In vineyard trials against *E. necator*, COS-OGA (37.5 g/ha) significantly reduced powdery mildew severity by 76–78% on grape bunches, which is comparable to sulfur fungicides under high disease pressure. Similarly, in greenhouse cucumber trials targeting *S. fuliginea*, it achieved a 69–72% reduction in severity at a leaf wall area of 25 g/ha, often outperforming chemical references. The elicitor's efficacy lasted for over one month post-application, supporting its integration into sustainable disease management programs as a low-residue alternative with minimal environmental impact [148].

Several microbial biocontrol agents are also approved. These utilize specific strains of Bacillus bacteria: *B. subtilis* strain IAB/BS03 (Fungisei), *B. amyloliquefaciens* strains QST 713 (Rhapsody), MBI600 (Serifel), and FZB24 (Taegro). Additionally, products based on plant extracts (Problad, containing water extract from sweet white lupin seeds) and yeast cell wall derivatives such as Romeo, containing cerevisane, are included.

Khalaf and Raizada [149] demonstrated that cucurbit seeds naturally harbor diverse endophytes with potent disease-suppression traits. A majority (70%) of 169 bacterial endophytes isolated from cultivated cucurbit seeds exhibited antagonism against major soil-borne fungal and oomycete pathogens (*Rhizoctonia solani*, *Fusarium graminearum*, *Phytophthora capsici*, *Pythium aphanidermatum*) in vitro, as well as the foliar pathogen *Podosphaera fuliginea*, which causes powdery mildew, in plants. *Bacillus* and *Paenibacillus* endophytes dominated the in vitro antagonists (68%), while *Lactococcus* and *Pantoea* displayed universal anti-oomycete activity, and *Pediococcus*/*Pantoea* were highly effective against powdery mildew. Notably, 67% of the isolates produced defense-inducing VOCs (acetoin/diacetyl) and 62% secreted extracellular ribonucleases.

B. amyloliquefaciens LJ02, which was isolated from greenhouse soil, demonstrated high efficacy (70–90% control) against cucumber PM (*P. fuliginea*) in greenhouse trials. LJ02 fermentation broth induced systemic resistance in cucumber plants, evidenced by a significant increase in the activity of defense enzymes (SOD, POD, PPO, PAL), elevated salicylic acid (SA) levels, and upregulation of the SA-dependent *PR-1* gene. Remarkably, the foliar application of fermentation broth also triggered long-range resistance extending to the rhizosphere, suppressing pathogens like *F. oxysporum*, *B. cinerea*, and *Alternaria* spp. Both LJ02 bacterial cells and fermented substances contributed to SA-mediated defense responses, suggesting that microbe-associated molecular patterns (MAMPs) play a key role in activating bidirectional (aboveground–belowground) systemic resistance [150].

In the case of *B. subtilis*, García-Gutiérrez et al. [97] found that strain UMAF6639 reduced CPM (*P. fusca*) by approximately 50% via root-mediated induced systemic resistance (ISR). This ISR activates both JA- and SA-dependent defense pathways, as demonstrated by the upregulated expression of JA-responsive *LOX2*, SA-responsive *PR1*, and defense-related *PR9* genes. Protection is abolished when JA signaling is inhibited by ibuprofen. The lipopeptide surfactin is the primary elicitor of this systemic resistance; surfactin-deficient mutants fail to confer protection, while synthetic surfactin restores disease suppression. Additionally, UMAF6639 primes plants for enhanced H₂O₂ production and callose/lignin

deposition at infection sites and directly antagonizes the pathogen in leaves through the production of iturin and fengycin [151].

In another study, Trupo et al. [152] demonstrated that cell-free supernatant (CFS) from *B. subtilis* ET-1, which is rich in the lipopeptide Iturin A (400 mg/L), effectively controlled CPM (*P. xanthii*) in melon. Greenhouse trials showed that 100% CFS (400 ppm Iturin A) completely suppressed disease symptoms, matching the efficacy of chemical fungicides, while field applications of 25% CFS or partially purified Iturin A extract (100 ppm) achieved 85–88% control, comparable to conventional treatments. The antifungal activity was attributed to Iturin A's membrane-disrupting action, presenting a low risk of resistance due to its physical mode of action [152].

It is not only bacteria that can control PM; the yeast-like fungus *Pseudozyma aphidis* demonstrated significant biocontrol efficacy against CPM (*P. xanthii*) through dual parasitism and antibiosis mechanisms. Greenhouse trials showed that the foliar application of *P. aphidis* (10^8 cells/mL) reduced disease severity by 75% at 16 days after inoculation and delayed symptom onset by 12 days. The fungus exhibited dimorphic behavior, transitioning from yeast-like cells on healthy tissue to hyphae that coil around pathogen hyphae (ectoparasitism), coupled with chitinase activity and the secretion of antifungal metabolites that inhibited >95% of *P. xanthii* spore germination on plants. Ultrastructural analysis revealed deformed cell walls, cytoplasmic disorganization, and the collapse of powdery mildew hyphae upon interaction with *P. aphidis*, highlighting its potential as a non-bacterial biocontrol agent [153].

Research has also shown that Cerevisane, which is derived from the cell walls of the *Saccharomyces cerevisiae* strain LAS117, has excellent potential in sustainably managing powdery mildew in crops. Its effectiveness stems from activating systemically acquired resistance pathways in host plants, which enhances its natural defenses against fungal pathogens, such as *Podosphaera* spp. With its favorable impact on the environment and minimal harm to non-target organisms, Cerevisane appears to be a promising component of integrated disease management strategies for controlling powdery mildew [154].

Beyond microbial agents, plant essential oils are also effective against *P. xanthii*. Greenhouse trials demonstrated that lemongrass, lemon, peppermint, and a blend of essential oils reduced disease severity by 65–77%. The oil blend performed best, matching the efficacy of chemical fungicides while enhancing plant physiology; it increased plant height, leaf area, biomass, chlorophyll a, carbohydrates, and proteins. In vitro analysis revealed that the oils cause dose-dependent hyphal deformation and conidial plasmolysis at concentrations of 2.0 mL/L or higher, with complete pathogen death observed at 2.5 mL/L. Importantly, the oils strengthened cell membrane stability but caused phytotoxicity (leaf shine and margin death) at concentrations above 3.0 mL/L, highlighting the critical concentration thresholds [155].

The encapsulation of plant essential oils within chitosan nanoparticles using nanotechnology is highly effective, presenting a sustainable strategy for managing CPM (*P. fusca*). Research demonstrates that both spinach seed essential oil (SSEO, dominated by *trans*-anethole) and celery seed essential oil (CSEO) exhibit significantly greater efficacy when nanoencapsulated in chitosan particles than in their non-encapsulated forms [156,157]. These nanoformulations utilize pH-dependent Fickian diffusion kinetics for controlled release, with faster essential oil liberation under acidic conditions (pH 3) and sustained, slower release at neutral pH (pH 7), thereby improving oil stability and prolonging activity. In vivo trials confirmed their dual-action mechanism: direct antifungal effects via the sustained release of bioactive oil components, coupled with the potent induction of systemic plant defense responses. This includes significant upregulation of key defense pathways—notably the phenylpropanoid pathway leading to increased flavonoids and

phenolics—and enhanced activity of critical enzymes like peroxidase (POX), polyphenol oxidase (PPO), phenylalanine ammonia-lyase (PAL), β -glucanase, and chitinase. Critically, both SSEO-LCNPs and CSEO-LCNPs triggered these defense mechanisms, not only in infected plants (peaking at 2–8 days post-application) but also systemically in healthy plants, indicating a priming effect for resistance. Overall, the nanoencapsulation approach markedly enhances the stability, controlled delivery, and bioactivity of these essential oils, positioning them as viable, eco-friendly biofungicide alternatives to synthetic chemicals for integrated disease management in sustainable agriculture [156,157].

6.4. Chemical Control

Chemical control, mainly through fungicides, is still a key tool for managing CPM, particularly when disease pressure is high or other methods are insufficient. However, its effectiveness is limited by the pathogen's tendency to develop resistance, as well as growing concerns about environmental and non-target effects. Consequently, careful selection, strategic timing based on monitoring, and rotation of fungicide modes of action are essential to maintain effectiveness and follow integrated management principles [136].

For the cultivation of cucurbits in greenhouses and in the field cultivation of cucurbits, spraying with registered fungicides should begin after the first symptoms of the disease appear. If necessary, treatments should be repeated every 7–14 days [158,159]. During the inspection of the plantation, mature leaves for powdery mildew infection should be observed [49,160].

A comprehensive and up-to-date list of registered plant protection products, including fungicides authorized for use against cucurbit powdery mildew in different countries, is available at the European and Mediterranean Plant Protection Organization (EPPO) database [161]. A detailed overview of fungicide options specific to Poland is included in the Supplementary Materials (Table S1).

In the USA, the following active ingredients are recommended for controlling CPM: triflumizole, prothioconazole (demethylation inhibitors), metrafenone, pyriofenone (aryl-phenyl-ketones) and fluopyram (succinate-dehydrogenase inhibitors) + tebuconazole (demethylation inhibitors) [160]. In Poland, alongside metrafenone, the following are recommended: azoxystrobin (quinone outside inhibitors), difenoconazole (demethylation inhibitors) + fluxapyroxad (succinate-dehydrogenase inhibitors), azoxystrobin + difenoconazole and sulfur (multi-site contact activity) [162].

Sulfur is the most frequently authorized active ingredient, typically formulated at 800 g/kg or 995 g/kg. Sulfur is one of the oldest known fungicides and has been used since the 19th century to combat powdery mildew. It works by disrupting the breathing of fungal spores and mycelia, making it effective as both a preventive and curative fungicide [163].

Kim et al. [163] showed that sulfur-based compounds, especially ultra-fine sulfur particles and lime sulfur (sulfur + calcium oxide), were highly effective in controlling cucumber powdery mildew (*P. fusca*) under greenhouse conditions. Control rates of 85.1% to 96.00% and 84.0% to 92.77% were achieved, respectively, which are comparable to those of the most effective mixtures. The authors noted that sulfur works by volatilizing on leaf surfaces and redistributing across plant tissues, disrupting fungal respiration. Sulfur-based treatments are reliable components of an integrated pest management strategy for powdery mildew and are viable for use in organic farming when applied preventively with sufficient frequency (2–3 applications) [163].

According to Jia et al. [164], applying sulfur powder is a cost-effective and environmentally friendly alternative to other fungicides and foliar sprays for controlling cucumber powdery mildew. Adding sulfur powder at a rate of 0.6 g/kg of soil significantly reduced the severity of the disease, lowering the disease index from 89 to 17.27 compared

to untreated controls. By increasing sulfur absorption, the plant's antioxidant capacity is enhanced (as shown by higher SOD and CAT enzyme activity), which reduces the accumulation of harmful reactive oxygen species (ROS) in leaves, and likely activates sulfur-dependent defense pathways, thereby improving resistance. Additionally, sulfur application promoted photosynthesis, increased fruit yield by 8.86%, and enhanced some fruit quality traits (higher soluble protein, titratable acid, and soluble solids), while having minimal negative impact on most soil enzyme activities [164].

In view of the widespread reports of *P. xanthii* fungicide resistance in other regions, the study by Hendricks and Roberts [165] evaluated the sensitivity of Florida squash and watermelon isolates to five key fungicides (thiophanate-methyl, myclobutanil, flutriafol, quinoxyfen, cyflufenamid) for powdery mildew management. Thiophanate-methyl failed to control *P. xanthii* in all assays, while quinoxyfen, myclobutanil, cyflufenamid, and flutriafol provided significant but incomplete control; no fungicide fully prevented pathogen establishment and sporulation at maximum labeled rates [165].

Another study evaluated isolates from the Midwestern US against five groups of fungicides: quinone outside inhibitors (azoxystrobin), phenylacetamide (cyflufenamid), succinate dehydrogenase inhibitors (penthiopyrad), quinolines (quinoxyfen), and demethylation inhibitors (triflumizole). This evaluation included laboratory bioassays with 37 isolates and four-year field trials on pumpkins. Laboratory sensitivity assays revealed widespread reduced sensitivity, with only 22% of the isolates sensitive to azoxystrobin, 57% to cyflufenamid, 54% to penthiopyrad, and 62% to triflumizole at the tested concentrations. However, quinoxyfen caused phytotoxicity, preventing laboratory evaluation. Furthermore, the field trials demonstrated that triflumizole and quinoxyfen were the most effective at controlling powdery mildew, significantly outperforming azoxystrobin, cyflufenamid, and penthiopyrad [166].

In the face of widespread fungicide resistance in powdery mildews such as *P. xanthii*, Martínez-Cruz et al. [69] identified fungal chitin deacetylase (CDA)—a key enzyme that converts the immunogenic compound chitin into the less-active compound chitosan—as a novel target for fungicide development. RNAi silencing of *PxCDA* in *P. xanthii* drastically reduced virulence by activating chitin-triggered immunity in the host plant (melon). This effect was reversed by co-silencing, which demonstrated the essential role of CDA in evading host immunity. Interestingly, ethylenediaminetetraacetic acid (EDTA) was found to effectively suppress powdery mildew disease by inhibiting CDA activity, as confirmed through molecular docking in the *Aspergillus nidulans* model, and subsequently eliciting chitin-triggered immunity. Its effect was independent of metal chelation and partially reliant on CmCERK1. Moreover, EDTA also controlled necrotrophic fungi (*B. cinerea*, *Penicillium digitatum*) on fruit, showcasing CDA's potential as a broad-spectrum fungicide target, with EDTA serving as a lead compound for the design of novel inhibitors against resistance [69].

Another study [167] used molecular topology (MT)—a chemo-mathematical QSAR method—to design new chitin deacetylase inhibitors in a rational way. Iterative MT modeling of topological descriptors identified promising CDA inhibitor candidates, and virtual screening prioritized certain compounds based on predicted activity and docking affinity to conserved residues (Tyr145, His206, Asp49) in the CDA catalytic pocket. At 100 μ M, three compounds significantly inhibited CDA enzymatic activity (65–93%) and suppressed powdery mildew, gray mold, and green mold in plants; importantly, their fungicidal effect depended on plant CERK1-mediated immunity activation, confirming a CDA-targeted mode of action. These μ M active compounds represent a novel class of fungicides targeting CDA. They are 200-fold more potent than EDTA and employ a resistance-busting mechanism that leverages host immunity [167].

6.5. Forecasting Model of Powdery Mildew Disease in Cucurbits

Losses caused by the disease make CPM forecasting models [168,169] important tools for managing disease. A weather-based Powdery Mildew of Cucurbit Simulation (POMICS) [168] model provides a simulation of disease progression and a prediction of fungicide application. These models help growers make informed decisions about fungicide applications, potentially reducing chemical use and minimizing the risk of fungicide resistance. More advanced techniques used for forecasting include the following:

- Machine Learning (e.g., CNN-LSTM): These models can fuse quantitative disease information with environmental data to predict disease incidence [170].
- Hyperspectral and Terahertz Technology: These methods use spectral data from leaves to detect and identify powdery mildew, even in its early stages [171].

7. Climate Change Impacts on Powdery Mildew

Global climate change, characterized by rising CO₂ levels, warmer temperatures, altered rainfall patterns, and more frequent extreme weather events, is dramatically altering the environmental factors that trigger plant disease outbreaks [172,173]. In the case of cucurbit powdery mildew, mainly caused by *P. xanthii* and *G. orontii*, these changes are re-defining the key factors in the spread of the disease, including the geographical distribution of the pathogen, its survival strategies during the winter months, its reproductive rate, its ability to infect hosts and the susceptibility of the host [174,175]. Understanding how these climate, pathogen, and host factors interact is crucial for devising disease management strategies that can withstand future climate changes.

Rising temperatures favor the thermophilic *P. xanthii* (optimal infection: 25.7 °C, sporulation: 22.3 °C) over the cooler-adapted *G. orontii*/*G. cichoracearum* (optimal infection: 17.3 °C, sporulation: 14.9 °C), resulting in a documented shift in pathogens in Central Europe. This is clearly evidenced in the Czech Republic, during the cooler period of 1979–1980 (average annual temperature: 7.4 °C; growing season: 15.7 °C), where *G. cichoracearum* dominated (86% of samples), while *P. xanthii* was rare and confined to warmer microclimates. By 1995–2007, following an increase in temperatures (avg. annual temp: 8.1 °C; growing season: 16.2 °C), *P. xanthii* was consistently present annually, often dominant in field crops and frequently found in mixed infections with *G. cichoracearum*, and expanded geographically into previously cooler regions like Bohemia and Moravia. This reflects a broader trend where *P. xanthii* prevalence rose significantly from 14% to a consistent annual presence across the region as average temperatures increased [29,43].

Warmer springs and autumns extend the infection period, enabling *P. xanthii* to overwinter or become established earlier in areas that were previously considered unsuitable. Within its optimal temperature range (10–32 °C), higher temperatures shorten latency periods and intensify sporulation, accelerating the entire disease cycle (germination, infection, sporulation) and facilitating the development of epidemics more quickly. This raises cumulative disease pressure by creating more favorable days per season. While temperatures above 35 °C inhibit germination, conditions at or below 30 °C significantly enhance growth and reproduction [29,43,176,177].

Both pathogens require high humidity (RH > 94–97.5%) for germination and infection, although *P. xanthii* tolerates slightly lower RH than *G. orontii*. Warmer air increases its capacity to hold moisture, potentially extending dew periods that are critical for infection. Although powdery mildew favors drier macro-conditions, warmer temperatures increase evapotranspiration, creating humid microclimates within dense canopies that support *P. xanthii*. Additionally, *P. xanthii* shows greater moisture tolerance during infection than was previously recognized. Heavy rain can wash off conidia, but post-rain humidity spikes

trigger new infections, while drought may concentrate leaf nutrients, thereby enhancing susceptibility [29,43].

Rising temperatures and increased disease pressure can stress host plants, potentially compromising their key resistance mechanisms. Elevated temperatures can weaken the phenylpropanoid pathway, reducing lignin and phenolic compounds and suppress ROS-scavenging enzymes (SOD, CAT, POD), which are crucial for defense against *P. xanthii*. While resistant cultivars exhibit stronger defense activation under pressure, susceptible plants experience higher disease incidence and severity in a warming environment, which directly reduces yield and fruit quality [8,43].

Warmer springs may cause phenological mismatches by advancing host development relative to pathogen peaks. Extreme weather adds volatility: heatwaves (>35 °C) suppress *P. xanthii* but induce heat stress in hosts, which could increase post-stress susceptibility. Meanwhile storms facilitate long-distance conidial dispersal. Warming combined with CO₂-driven canopy densification may synergistically enhance favorable microclimates; however, the CO₂-specific effects require further quantification. These interactions significantly complicate disease management strategies [8,29,43].

Climate change, primarily due to rising temperatures, is driving a significant shift towards more aggressive and thermotolerant pathogens. This shift increases disease risk through an earlier seasonal onset, accelerated epidemics, geographic expansion into previously cooler regions, and prolonged favorable infection windows. At the same time, host defense mechanisms may be weakened under thermal stress, further complicating management challenges. Effective adaptation requires the following: (1) pathogen-specific thermal models that leverage distinct temperature optima; (2) the development of climate-resilient host resistance; and (3) dynamic fungicide programs that respond to evolving pathogen dynamics and increased disease pressure.

8. Future Perspectives

As global climate change continues to alter environmental conditions, the impact of this change on the epidemiology and severity of powdery mildew in cucurbitaceous crops is becoming increasingly relevant. Rising temperatures, shifting humidity patterns, and altered precipitation regimes are expected to increase the prevalence and virulence of *P. xanthii* and *G. orontii*, potentially expanding their geographic range and complicating existing management strategies. Future research must therefore integrate climate-resilient disease forecasting models with molecular breeding approaches. Continued exploration of the molecular dialogue between cucurbit hosts and powdery mildew pathogens will be critical to developing durable and broad-spectrum resistance. Future research should prioritize the functional characterization of newly identified susceptibility (S) and resistance (R) genes, as well as the molecular profiling of effector repertoires across diverse *P. xanthii* and *G. orontii* isolates. Leveraging high-throughput sequencing, CRISPR/Cas-based genome editing, and multi-omics integration can accelerate the identification of gene networks modulating resistance. Furthermore, understanding how environmental variables and microbiome interactions influence host–pathogen dynamics could lead to the development of more holistic, agroecological management strategies. Combining genetic resistance with agronomic practices and predictive disease modeling could provide sustainable solutions for controlling powdery mildew under changing climate conditions.

9. Conclusions

PM remains a significant obstacle to the sustainable production of cucurbits, a problem that is being exacerbated by the effects of climate change. While significant progress has been made in understanding the molecular basis of host resistance and pathogen

virulence, the complex interaction between genetic, environmental, and epidemiological factors necessitates a multifaceted approach. Incorporating climate-resilient breeding targets, molecular diagnostics, and adaptive disease management strategies is essential for mitigating future disease outbreaks. The convergence of genomics, gene editing, and predictive modeling offers hope for the development of long-lasting, environmentally responsive resistance in cucurbits. Ultimately, translating molecular insights into climate-smart crop improvement programs will be vital for ensuring food security and agricultural sustainability in the face of a rapidly changing global climate.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/agriculture15161743/s1>, Table S1: Authorized plant protection products for cucurbit crops against powdery mildew in Poland.

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