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Molecular Mechanisms and Cytopathology of Phytophthora: Strategies, Interactions and Future Perspectives

Aswathi M. S [a++*], Lellapalli Rithesh [a++*] and N. V. Radhakrishnan [a#]

[a] Department of Plant Pathology, College of Agriculture, Kerala Agricultural University, Vellayani, Thiruvanathapuram, 695522, Kerala, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author AMS conceptualized the study and wrote original draft of the manuscript. Author LR wrote, reviewed and edited the manuscript. Author NVR reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Phytophthora is an aggressive plant pathogen, pose substantial threats to global agriculture, leading to extensive crop losses. Controlling *Phytophthora* diseases remains challenging, with limited effective methods available. Host resistance emerges as a promising strategy, but its sustainability hinges on a profound comprehension of the intricate molecular dynamics governing *Phytophthora*-plant interactions. These interactions unveil a hemi-biotrophic lifestyle of *Phytophthora*, transitioning from biotrophic to necrotrophic phases during infection. The infection process involves a series of orchestrated events, including chemotactic attraction, penetration, and

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[++] *Ph.D. Scholar;*
[#] *Professor;*
**Corresponding author: E-mail: msaswathi95@gmail.com; rithesh132@gmail.com;*

sporulation on the host surface. Molecular cytology elucidates a sophisticated interplay between *Phytophthora* and plant defense mechanisms. *Phytophthora* elicits defense responses in host plants through the release of elicitor molecules, triggering PAMP Triggered Immunity (PTI) responses such as antimicrobial compound production and cell wall fortification. Detection and recognition of *Phytophthora* effectors instigate a second layer of defense in resistant plants, leading to Effector Triggered Immunity (ETI) and hypersensitive response. In response, virulent strains evolve altered effectors to evade detection and suppress host defenses, underscoring the ongoing molecular coevolution between *Phytophthora* and plants. The pathogenic success of *Phytophthora* species is attributed to their diverse and rapidly evolving effector gene complements, targeting various host proteins and cellular processes. Future strategies for combating *Phytophthora* diseases include genome editing using CRISPR/Cas-9 technology to enhance plant immunity and the identification of non-race-specific resistance sources for broad-spectrum protection. In essence, a comprehensive understanding of *Phytophthora*-plant interactions at the molecular level is imperative for devising effective strategies to mitigate their impact on global agriculture.

Keywords: Phytophthora; plant defense mechanisms; effector proteins; host genetic resistance.

1. INTRODUCTION

The genus *Phytophthora* has drawn a lot of interest due to its ability to cause diseases in crops that are significant to the economy. *Phytophthora* comprises more than 60 species, many of which are highly pathogenic plant diseases that severely damage horticultural, and agricultural crops [1]. Certain species, including *Phytophthora sojae*, which causes soybean root rot, and *Phytophthora infestans*, which causes late blight in potatoes, have a restricted host range. Some diseases, including *Phytophthora nicotianae* and *Phytophthora cinnamomi*, have very wide host ranges; they may infect more than a thousand distinct plant species [1,2].

Phytophthora is a member of the *oomycetes* class and the Kingdom *Chromista*. They generate biflagellate, asexual spores known as zoospores, which are primarily responsible for the initiation of plant infection. According to Hardham and Hyde [3], the zoospores develop within a multinucleate cell known as a sporangium, which then cleaves to produce and release the uninucleate zoospores. Fungal conidia and *Phytophthora* sporangium have superficial similarities. During vegetative development, several *Phytophthora* species produce hyphae that mimic fungi in both appearance and lifestyle.

Since their structure, biology, and pathology are fundamentally different from those of actual fungus, management strategies that work for true fungi often fail to work against *Phytophthora*. A thorough knowledge of the infection process at the cellular and molecular level will be crucial to the development of long-term control strategies for *Phytophthora* infections. Host genetic resistance deployment is seen to be the most economical, environmentally responsible, and successful management tactic. Understanding the molecular ground works of *Phytophthora*-plant interactions in great detail is crucial for developing long-lasting resistance to *Phytophthora* [4]. By identifying the essential elements of *Phytophthora* pathogenicity at the molecular and cellular level, it could subsequently be feasible to enhance capacities for accurate diagnosis, potent chemical control agents, resistant plant germplasm, and *Phytophthora* management procedures.

2. INFECTION STRATEGIES AND LIFESTYLES

Phytophthora spp. are hemi-biotrophic, which means they create a biotrophic association with their host plant. They spread through the cortex in this manner; however, necrotrophy is evident after *Phytophthora* is well-established and hyphae have penetrated the endodermis and vascular system [5]. The pathogen contacts the plant during the infection phase and adheres itself firmly to the plant's surface. Then, after penetrating the host's surface, it colonizes the plant, obtaining the nutrients required for development and sporulation in the process. The cycle restarts when spores are created and released [6]. The general infection cycle of *Phytophthora* spp. causes various diseases is illustrated in (Fig. 1).

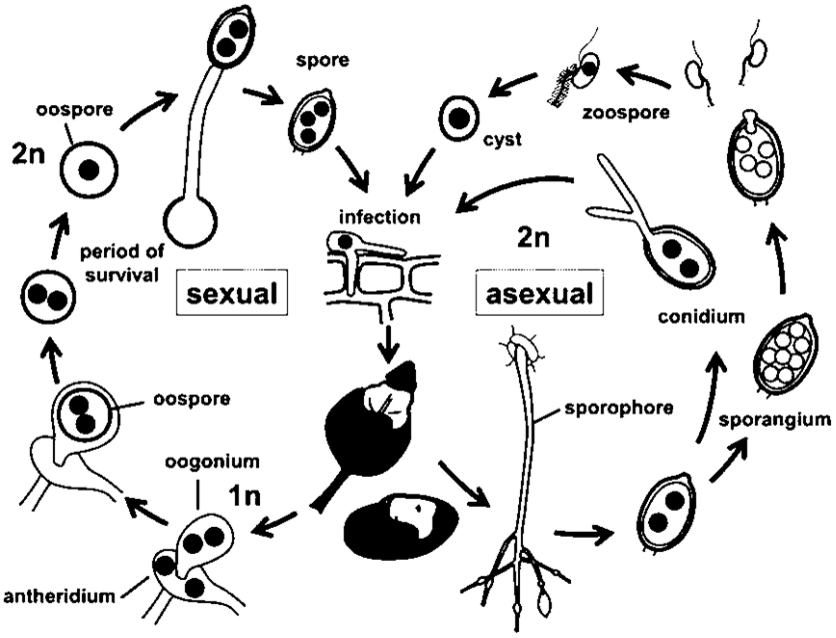

Fig. 1. The general infection cycle of *Phytophthora* spp. (M. Piepenbring)

3. MOLECULAR CYTOLOGY OF *PHYTOPHTHORA* – PLANT INTERACTIONS

3.1. General Plant – pathogen interactions

The pathogen associated molecular pattern (PAMP)-triggered immunity (PTI) layer is the first of two levels of induced defense, according to the zigzag model of plant pathogen interaction. Plant pattern recognition receptors (PRRs) in PTI detect conserved chemicals or structures of pathogens, which trigger the activation of defensive mechanisms. Pathogens transport effector proteins into host cells, where they impede defensive responses, therefore evading PTI. Through resistance (R) genes, plants are able to identify effectors and then initiate a more robust and rapid defensive response known as effector-triggered immunity (ETI). Pathogens are able to effectively infect susceptible hosts when one or more pathogen effectors block PTI. When this happens, ETI is finally overcome in the absence of efficient R proteins, which results in effector triggered susceptibility (ETS). The coevolution of effectors in pathogens and matching R genes in plant hosts results in several shifts between ETS and ETI [7,8].

3.1.1. *Phytophthora* - plant interactions

Plants detect a broad range of elicitors in order to identify *Phytophthora* spp. Originally, exogenous and endogenous signaling molecules that may trigger any kind of defensive response in plants were referred to as "elicitors" [8,9]. Exogenous elicitors are the components of the pathogen's cell wall or membranes that are secreted by the pathogen during host-pathogen contact, released following the action of host enzymes, or both in order to undermine the host defense and/or promote the acquisition of nutrients [10]. On the other hand, components known as endogenous elicitors were derived from host plants and often resulted from damage induced by pathogen enzymes. The labels "endogenous" and "exogenous" elicitors were commonly termed also as "Damage Associated Molecular Patterns (DAMPS)," or PAMPs. The BRI1-associated kinase 1 (BAK1)/SERK3 domains, which are members of the small somatic embryogenesis receptor kinase (SERK) family, mediate the perception of the *Phytophthora* elicitors [11]. These are the cell surface receptors of the Leucine Rich Receptor-Receptor-like Kinase (LRR-RLK) type that are found on the plasma membrane of host cells and that may initiate a signaling pathway in host plants.

3.2 *Phytophthora* elicitors

Plants detect a broad range of elicitors in order to identify *Phytophthora* spp. Table 1 lists the elicitors of *Phytophthora* spp. and the PTI components that are related to them.

Table 1. *Phytophthora* spp. elicitors and associated PTI components

Name	Chemical Nature	Cognate PRR	PAMP Perception Model
Elicitins	Protein	Elicitin response receptor (ELR)	BAK1/SERK3 dependent
OPEL	Protein	Unknown	Unknown
Pep-13	Protein/peptide	Unknown	Unknown
β-glucans	Carbohydrate	CERK1 (Chitin elicitor receptor kinase 1)	Unknown
NLPs	Protein	RLP23 (Receptor Like Protein)	BAK1/SERK3 dependent
CBEL	Protein	Unknown	BAK1/SERK3 dependent

3.2.1 Pep-13

The elicitor Pep-13, a 13-amino-acid peptide of a transglutaminase protein's surface-exposed region, was identified from *P. sojae*. The perception is independent of BAK1/SERK3. Promotes the formation of crosslinks between lysine and glutamine residues in proteins to fortify structures like cell walls. Transglutaminase activity and the activation of plant defenses are both dependent on the Pep-13 motif [12]. When Pep-13 infiltrates potato plant leaves, it causes necrosis development, hydrogen peroxide buildup, defense gene expression, and the production of salicylic and jasmine acids [13].

3.2.2 Elicitins

Elicitins are cysteine-rich extracellular structurally conserved proteins that have the ability to bind sterol and function as elicitors. Cryptogein from *P. cryptogea*, CAP1 from *P. capsici*, INF1 from *P. infestans* [14], ParA1 from *P. parasitica*, and PAL1 from *P. palmivora* are a few of the sterol binding elicitors. The elicitin response receptor (ELR), a wild potato receptor-like protein (RLP), is responsible for their perception. It interacts with BAK1 (BRI1-associated kinase 1) domains to provide broad-spectrum recognition. Since *Phytophthora* are unable to synthesize sterols, they must depend on the sterols provided by their hosts. They may have done by using elicitins, since they have evolved effective sterol scavenging strategies from host cell membranes [5,15]. They induce necrosis [16] and trigger signaling pathways regulated by ethylene and jasmonate [17]. Tomato leaf ethylene levels rose dramatically as a result of INF1 infiltration.

3.2.3 OPEL (Oligopeptide elicitor)

Another distinct oomycete-specific PAMP is called OPEL, and it was found in *P. parasitica*. It shares homologs with many *Phytophthora* species. A signal peptide and three conserved domains a glycine-rich protein domain, a thaumatin-like domain, and a glycosyl hydrolase domain with an active laminarinase site make up the 556 amino acid big modular protein known as OPEL. This laminarinase active site is linked to OPEL's elicitor activity, which a PRR may detect directly or indirectly by way of DAMPs produced by the enzyme's enzymatic activity. Callose deposition, cell death, the production of reactive oxygen species (ROS), and the induction of salicylic acid-responsive defense genes and PAMP-triggered immunity (PTI) response marker genes were all brought about by the infiltration of OPEL proteins into *Nicotiana tabacum* leaves. These events are indicative of a plant defense response. Applying stain using [18]. According to Chang et al. [18], treatment with OPEL (0.1 or 0.3 μM) caused a noticeable buildup of H_2O_2 by staining with 3,3'-diaminobenzidine (DAB) six hours after treatment.

3.2.4 Cellulose-binding elicitor lectin (CBEL)

CBEL is an apoplastic elicitor with lectin-like hem agglutinating activity and two carbohydrate-binding modules from family 1 (CBM1) domains which is present in *P. parasitica*. This allows the elicitor to bind to cellulose [19,20]. Commonly found in oomycete and fungal proteins are CBM1 domains. Fungal proteins that include CBM1 are involved in the breakdown of plant cellulose, whereas oomycetes' proteins, including CBEL are involved in adhesion [21]. Tobacco cells exhibit downstream signaling after CBEL perception, however protoplasts without a cell wall do not exhibit this signaling, indicating that plant cell wall binding is necessary for CBEL-induced defensive responses. CBEL was discovered to be present in close proximity to the host cell wall during infection and to be located in both the inner and outer layers of the cell walls of *Phytophthora* [22]. Defense proteins like PR-1, PDF1.2, and hydroxyproline-rich glycoprotein (HRGP) accumulate when CBEL stimulates the expression of multiple defense genes encoding lipoxygenase, peroxidase, sesquiterpene cyclase, basic glucanase, and anthranilate synthase [21,23,24].

In order to investigate the elicitor activity of recombinant CBEL, infiltrated tobacco leaves mesophyll. Four to five hours after infiltration, the infiltrated region on the abaxial face became somewhat bright. Nine to twelve hours later, the infiltrated area began to desiccate, and by the twenty-fourth hour, it had completely dried up. After that, the necrosis became brown and stayed confined to the region that had been invaded [21].

3.2.5 Necrosis and ethylene inducing proteins

Another example of PAMP effector overlap is the presence of ethylene-inducing peptide 1-like proteins (NLPs) and necrosis, which have been identified as common oomycetes elicitors that initiate defense responses in susceptible as well as resistant plants [25]. *Phytophthora* also has a wide distribution of NLPs. *P. nicotianae* NPP1 [26], *P. infestans* PiNPP1.1, and *P. sojae* PsojNIP are among the well-researched NLPs. The expression of NLP genes in *P. sojae* occurs late in the host infection process, which is in line with their role in inducing necrosis of host cells during the necrotrophic phase [27]. RLP23, a receptor-like protein, interacts with BAK1 to perceive them. According to Böhm et al. [28], they activate genes related to signal perception, such as ethylene signaling, reactive oxygen species (ROS) signaling, salicylic acid (SA) signaling, and mitogen activated kinase. NLPs feature a necrosis-inducing domain in their structure, which causes lipid bilayers to become toxic.

3.2.6 Beta-glucans

PAMPs known as beta-glucans are produced by host glucanases from *Phytophthora* cell wall components [29]. The two main substances that make up the cell walls of *Phytopthora* are β-1,3- and β1,6-glucan. CERK1, also known as Chitin Elicitor Receptor Kinase 1, functions as the PRR for β-glucans produced from *Phytophthora* spp. They have the ability to trigger defensive responses, such as an increase in the concentration of cytosolic calcium, the generation of reactive oxygen species (ROS), and the activation of signal transduction-related genes like MAPKs. They may also initiate the synthesis of phytoalexins.

3.3 Cytopathological Changes During PTI

The PTI response to *Phytophthora* consists of a number of defensive mechanisms, including as the deposition of callose to stop *Phytophthora* from penetrating, the deposition of lignin to strengthen the cell wall, and the synthesis of other defense molecules like phytoalexins. Zeyen et al. [30] investigated the cytopathological alterations that occurred when *P. sojae* infected a soybean root. They saw the wall appositions being deposited next to the hypha. Similar to this, *P. cinnamomi* hyphae that were developing in between two epidermal cells caused callose-containing deposited cell wall appositions in the plant epidermal cells. According to Vandana et al. [31], *P. capsici* causes lignification in black pepper root cells.

3.4 Effects of *Phytophthora* spp.

To maintain a close relationship with the host plant, *Phytophthora* has to stifle immunological reactions caused by their own elicitors. Pathogens modify the physiological state of plants to facilitate colonization by secreting effector proteins that have the ability to operate in several cellular compartments. Effectors are defense network manipulators and adaptability factors. Consequently, an N-terminal signal peptide that facilitates secretion from the bacterium is present in the majority of *Phytophthora* effectors that have been discovered. Apoplastic effectors and cytoplasmic effectors are the two different kinds of effectors. Whereas cytoplasmic effectors enter the plant cell and must pass through the extrahaustorial membrane and the plant cell wall, or alternately, the extrahaustorial matrix and the extra-haustorial membrane, apoplastic effectors work in the apoplast surrounding plant and microbial cells after they are released.

3.4.1 Apoplastic effectors

Plant-pathogen interactions takes place in the apoplast of the plant. Plants secrete many different catalytic proteins to the apoplast in defense against Phytophthora, either in response to PTI activation or as a prepared defense. *Phytophthora*'s apoplastic effectors manipulate plant cell protease-mediated immunity by inhibiting resistance-related proteases that are produced during PTI from plant apoplasts. To suppress the defense mechanisms of Phytophthora Inhibited Protease 1 (PIP1) in tomato plants, *P. infestans* secretes the cystatin-like cysteine protease inhibitors EPIC1–EPIC4 and EPIC2B [32]. *Hevea brasiliensis* serine protease (HbSPA) uses extracellular serine protease inhibitor (PpEPI 10) from *P. palmivora*

to overcome defenses [33]. Aspartic protease GmAP1 released by the host was able to bind with apoplastic effector PsAvh240 of *P. sojae* in the plant plasma membrane, preventing it from entering the apoplast and reducing soybean immunity [34]. Soybean glucanase GmGIP1 has the ability to suppress PsXEG1, another endogenous apoplastic effector of *P. sojae*. However, the pathogen may overcome this inhibition by secreting PsXLP1 effector, which has no active enzymatic activity [35]. PsXEG1 may be released to increase *P. sojae* pathogenicity on soybeans when PsXLP1 binds to GmGIP1 more firmly than PsXEG1. Table 2 lists apoplastic effectors and the proteases that are their target host.

3.4.2 Cytoplasmic effectors

An N-terminal signal peptide is followed by an RXLR (arginine-any amino acid-leucine-arginine) motif in most cytoplasmic *Phytophthora* effectors that have been described so far. This motif is expected to facilitate translocation into plant cells. To facilitate effector endocytosis, RXLR domains bind extracellular phosphatidylinositol-3-phosphate (PI3P) [34]. An EER motif and related motifs like QXLR and RXLQ may also come after the RXLR motif. Because RXLR expression is elevated during preinfection and biotrophic stages of infection, they are adapted to promote biotrophy. Effectors that include RXLRs fall into two primary functional categories. Although it is not necessary for effector action, the N-terminal domain, which contains the signal peptide and RXLR motif, aids in secretion and translocation into the host cytoplasm. Effector activity inside the host cells is carried out by the residual C-terminal region [36,37].

The CRinkling and Necrosis (CRN) protein family is a second class of *Phytophthora* effector proteins that are translocated into the plant cytoplasm. They exhibit necrosis and leaf crinkling, as well as the activation of genes related to the defense response [38]. In *Phytophthora*, CRNs constitute a complex family of rather big proteins (400–850 amino acids) [39]. Although the conserved N-terminal LXLFLAK motif in *Phytophthora* CRN proteins has some similarities to the RXLR sequence, none of the CRN proteins carry the RXLR motif [36]. Following their entry into the host cytoplasm, the CRN effectors alter cellular processes inside the host to produce macroscopic phenotypes such tissue browning, cell death, and chlorosis [40].

3.5 Effectors of *Phytophthora* - powerful Weapons for Manipulating Host Immunity

The *Phytophthora* species effectors are crucial for subduing plant defense mechanisms. Numerous *Phytophthora* effectors have been discovered in recent years, and an analysis of their targets and roles in plant cells has been conducted. Effectors of *Phytophthora* modulate several facets of plant defense mechanisms and modify the host's immunity to facilitate the infection.

3.5.1 Modulation of vesicle trafficking and secretion

Certain RXLR effectors are reported to interfere with the plant secretory pathway and vesicle-trafficking intracellularly, to suppress the secretion of proteases and other antimicrobial compounds to the apoplast, in addition to modulating apoplastic immunity through the apoplastic protease inhibitor effectors in the apoplast. For instance, it has been revealed that the *P. infestans* RXLR effector Avr1 interacts with the exocyst complex member (Sec5) to manipulate exocytosis. It was discovered that Avr1 was positioned around the perihaustorial membrane in the host cell with Sec5-associated mobile bodies, most likely to prevent it from joining the exocyst complex. Sec5 has been identified as a necessary element for PTI, and it has been proposed that the Avr1-Sec5 interaction disrupts PR-1 secretion and callose deposition, hence reducing host resistance against *P. infestans* [16]. According to reports, RxLR24, another highly conserved effector, interacts with members of the RABA GTPase family and may be implicated in the vesicular secretion of key antimicrobials such as defensin (PDF1.2) and PR-1 to promote infection [41].

3.5.2 Manipulating endoplasmic reticulum-mediated immunity

The crucial factor influencing the development of PTI responses is the endoplasmic reticulum (ER)-mediated stress response. It has been discovered that a number of RXLR effectors inhibit this ER-mediated immunity in various ways. By inhibiting the transcriptional regulation of defense components, *P.* infestans RXLR effector Pi03192 increases host susceptibility to the parasite by targeting two *N. benthamiana* NAC transcription factors at the ER membrane and preventing their localization to the nucleus [42]. It was discovered that the ER stress

Table 2. Apoplastic effectors and their target host proteases

Pathogen	Effector	Target
P. infestans	Cystatin-like cysteine protease inhibitors EPIC1-EPIC4 and EPIC2B	*Phytophthora* Inhibited Protease 1 (PIP1)
P. palmivora	Extracellular serine protease inhibitor (PpEPI 10)	*Hevea brasiliensis*serine protease (HbSPA)
P. sojae	PsAvh240	Host secreted aspartic protease GmAP1
P. sojae	PsXLP1, PsXEG1	GmGIP1

sensing protein FKBP15-2, which encodes a peptidyl-prolyl cis-trans isomerase (PPIase), interacted with the *P. capsici* RXLR effector PcAvr3a12 (Avr3a class). The connection between PcAvr3a12 and FKBP15-2 attenuates the ER-mediated defensive response against *P. capsici* by inhibiting FKBP15-2 stress sensing activity [43].

3.5.3 Manipulating phytohormone-mediated immunity

The signaling mechanisms for phytohormones are crucial for plant disease resistance. Specifically, a complex signaling network that controls plant resistance to harmful microorganisms is formed by auxin, ethylene (ET), jasmonic acid (JA), and SA. According to Liu et al. [44], the *P. sojae* effector PsIsc1 has the ability to hydrolyze host isochorismate and regulate SA metabolism, which lowers host SA levels and suppresses immunity. penetration-specific effector 1 (PSE1) OF *P. parasitica* may modify auxin contents at penetration sites and promote infections because its transcript is momentarily accumulated during the penetration of host roots [45]. In order to reduce JA and SA accumulation and suppress host immunity, the *P. infestans* effector PexRD24 (Pi04314) interacts with three protein phosphatase 1 catalytic (PP1c) isoforms necessary for disease development and induces their re-localization from the nucleolus to the nucleoplasm [46]. Yang et al. [47] have revealed that the ET biosynthesis pathway is a crucial defensive mechanism in soybeans against *P. sojae* infection. *P. sojae* uses PsAvh238—an RXLR effector that interacts with the host's ACSs (aminocyclopropane carboxylic acid synthases) to undermine ET-mediated defense. By catalyzing an essential step in the ET biosynthesis process, ACSs support plant defense. It has been shown that PsAvh238 destabilizes ACSs to inhibit the host's synthesis of ET and so encourage infection [47].

3.5.4 Manipulating MAPK-mediated immunity

Mitogen-activated protein kinase (MAPK) cascades, which are a highly conserved signaling pathway in all eukaryotes, may transport extracellular signals into cells via protein phosphorylation and dephosphorylation mediated by MAPK kinases (MAPKKs) and MAPKK kinases. The control of plant defense mechanisms against pathogens is largely dependent on the MAPKs. In order to inhibit activity, the *P. infestans* RXLR effector PexRD2 interacts with the MAPK kinase domain [48]. The MAPK signaling pathway is manipulated by the *P. sojae* RXLR effector, Avh331, to encourage the infection of *A. thaliana* and *N. benthamiana.* Significantly less H_2O_2 buildup and callose deposition are seen during this procedure [49].

3.5.5 Modulation of host's cell wall to plasma membrane continuum

The triggering of several PTI responses, including as callose deposition, ROS burst, and cell death, and cell wall sensory signaling depend on the adhesion of plant cell walls and plasma membranes. Plants may become more vulnerable to infections as a result of the damaged plasma membrane–cell wall adhesions. It is well recognized that peptides with the RGD (R = arginine; G = glycine; D = aspartic acid) pattern may break down CWPM adhesions in plants. It has been discovered that Avrblb1 (IPI-O1), a *P. infestans* RXLR effector that also has an RGD motif, disrupts CW-PM adhesion by going after LecRKI.9, a lectin receptor kinase associated with the plasma membrane. As a consequence, callose was deposited between the plasma membrane and the cell wall, disrupting the adhesions between the two [50].

3.5.6 Manipulating RNA interference-mediated immunity

One significant defensive mechanism that host plants use is called RNA interference, or RNAi.

The RNA silencing mechanism is suppressed by *Phytophthora* effectors, namely *Phytophthora* Suppressor of RNA Silencing 1 and 2 (PSR1 and PSR2). According to reports, PSR1 targets PINP1 (PSR1-Interacting Protein 1), a host RNA helicase that controls the build-up of endogenous microRNAs and small interfering RNAs (siRNAs) in Arabidopsis [51]. By interacting with a crucial part of the host's RNA silencing apparatus, double stranded RNA binding protein (DRB4), which is known to be involved in the production of secondary siRNAs, the PSR2 effector from *P. capsici* was discovered to block the host-induced pathogen's gene silencing [52].

3.5.7 Manipulating E3 ubiquitin ligase-mediated immunity

In eukaryotic organisms, the ubiquitin proteasome system is the most significant mechanism for protein degradation. In plants, it controls growth, development, and responses to both biotic and abiotic stressors. The enzymes E1 ubiquitin-activating enzyme, E2 ubiquitin-binding enzyme, and E3 ubiquitin ligase catalyze a sequence of events known as ubiquitination. Plants' normal protein degradation pathway is regulated by the *P. infestans* effector AVR3a, which interacts with and suppresses the activity of the U-box E3 ligase CMPG1 [53]. Table 3 lists the *Phytophthora* spp. effectors that alter host defensive responses in order to create ETS.

3.6 Cytopathological changes in host plant during ETS

Numerous enzymes that break down cell walls, such as endopolygalacturonases, are secreted by *Phytophthora* and are capable of breaking down the pectin found in the central lamella of the cells. Cell rupture will ensue from this, and signs such as water-soaked lesions, necrosis (rot), and cell death may appear. According to the research by Wu [54], *P. palmivora* causes infection-related disruptions to the sour orange cells' plasma membrane. On trifoliate orange, where there was no infection, *P. palmivora* did not cause any damage of the cell's plasma membrane. According to research on the histopathological reactions in susceptible *Capsicum annum* infected with *P. capsica*, Piccini et al. [55] found that the pith, phloem, and xylem of certain infected susceptible plants had significant damage.

3.7 Effector detection and recognition

NB-LRR proteins, which contain a nucleotide binding site and a leucine-rich repeat domain, are responsible for the cytoplasmic manner of direct and indirect effector detection and identification [56].

One of the biggest gene groups in the kingdom of plants is made up of the genes that encode these proteins; these genes are referred to as disease resistance genes, or R-genes. Numerous R-proteins that provide resistance against *Phytophthora* have been found and cloned. Potatoes' R1 and R3a genes provide resistance against *P. infestans*. Most NB-LRR proteins contain a nuclear localization signal, and they are cytoplasmic constituents. It has been suggested that they repress basal defense by interacting with a WRKY transcription factor, since they have been shown to migrate into the nucleus, in order to activate the expression of defense [57].

3.7.1 The second layer of defence is triggered by the recognition of *Phytophthora* effectors

Basal defence mechanisms do not always successfully inhibit *Phytophthora* ingress but plants have a second system of resistance that involves the recognition of specific pathogen molecules and the consequent induction of programmed cell death, also referred to as the hypersensitive response. As in fungal-plant interactions, hypersensitive cell death is a highly effective means of restricting pathogen growth and development. In *Phytophthora*–plant interactions the main classes of molecules that induce the hypersensitive response are effectors. Effector-triggered hypersensitive resistance is a widespread response induced by race-specific proteins from *Phytophthora* [37,58]. In resistant plants, these effectors are avirulence proteins that are recognised either directly or indirectly in a gene for-gene-specific manner by resistance proteins [59]. R1, R3a, and R4 are among the 11 major dominant R genes introgressed from *Solanum demissum* into different potato cultivars against *P. infestans*. Table 4 shows some of the *Phytophthora* effectors (avr) and their corresponding R proteins.

Table 3. *Phytophthora* effectors that modulate host defense responses

Effector	*Phytophthora* spp.	Host Target	Virulence Function to Establish ETS
Avr1	*P. infestans*	Sec5 Exocyst subunit	Prevent PR-1 secretion and callose deposition
RxLR24	*P. infestans*	RABA GTPase	Prevent secretion of PR-1 and defensin (PDF1.2)
Pi03192	*P. infestans*	NAC transcription factors	Prevent NAC localization from ER to nucleus
Avr3a12	*P. capsici*	FKBP15-2	Inhibits ER stress sensing
PsIsc1	*P. sojae*	Host isochorismate	decreasing SA levels in hosts
Pi04314	*P. infestans*	PP1cs	Modulate JA and SA signaling
PsAvh238	*P. sojae*	ACSs	Suppress ET biosynthesis
Avh331	*P. sojae*	MAPK	Interferes with MAPK signaling
Avrblb1/IPIO1	*P. infestans*	LecRK-1.9 Lectin receptor kinase	Disrupt cell wall to plasma membrane continuum
PSR2	*P. capsici*	RNA binding protein DRB4	Modulates RNA silencing
PSR1	*P. sojae*	PINP1 RNA helicase	Suppress RNA silencing
Avr3a	*P. infestans*	CMPG1 E3 ligase	Prevent ubiquitin-dependent proteolysis

Table 4. *Phytophthora* effectors and their corresponding R proteins

Effector (Avr)	R genes
P. infestans RXLR effector Avr1	R1
P. infestans RXLR effector Avr3a	R3a
P. sojae RXLR effector Avh1b	R3a
P. sojae Avr1b	Rpi1b
P. infestans PiAvrblb2	Rpi-blb2

In order to cause ETI, R1 identifies P. infestans RXLR effector Avr1. R3a recognizes Avr3a, the RXLR effector. Avh1b, the *P. sojae* RXLR effector, is discovered to be recognized by R3a and has sequence similarities with Avr3a. Rpi-blb2, a R gene found in *S. bulbocastanum*, is capable of identifying *P. infestans* PiAvrblb2. PiAvr2 is recognized by Rpi genes, which then strongly stimulate HR.

In *N. benthamiana* leaves, Bos et al. [37] investigated the relationship between R3a and the AVR3a proteins. AVR3aKI causes a fast cell death response when combinations of *Agrobacterium tumefaciens* strains expressing R3a and the AVR3a proteins are infused into *N. benthamiana* leaves. AVR3aKI is recognised particularly by R3a, but not by its paralog (R3-1). These findings show that, among the NBSLRR genes of the R3 locus that have been studied, AVR3aKI is particularly recognized by R3a.

3.8 *Phytophthora* Counter-defence

Although the whole scope of pathogen effectors' involvement is still being investigated, evidence suggests that they play a part in defense mechanisms suppression, recognition avoidance, chemical defense resistance protection, and the regulation of metabolic and structural changes in plant cells. To inhibit the ETI and evade detection by the corresponding R genes in the host, virulent strains of *Phytophthora* produce modified or novel effector molecules. The protein architectures of virulent and avirulent Avr2 variants vary, and virulent Avr2 are really intrinsically disordered proteins (IDPs). Because IDPs feature intrinsically disordered regions (IDRs), these proteins may have benefits over structured proteins in terms of both function and evolution. Variants of IDP-type Avr2 are expected to be unstable and have short half-lives for proteins. According to Yang et al. [60], the authors propose that these characteristics allow pathogenic variants of Avr2 effectors to avoid being identified by R2. This is an excellent example of effector evolution to generate ETS and avoid ETI. The virulent isolates of *P. infestans* on potato plants having R1 do not have Avr1, but they do have a homologous gene called Avr1-like (Avr1-L) effector, which is not recognized by R1 because

of a loss of potent domains at the C terminus [61]. Similar to this, shortened and non-functional homologous avr4 alleles are carried by *P. infestans* isolates that are virulent on potato cultivars containing the R4 gene [62]. Both effectors and elicitors-induced hypersensitive cell death may be inhibited by them. According to Wang et al. [58], the interaction between R3a and Avr3a is what causes the novel effectors Avh172 and Avh6 to reduce the hypersensitive response.

3.8.1 Rapidly evolving effectors

Numerous quickly changing effectors are carried by *Phytophthora* spp., which helps them go beyond ETI and into the second stage of ETS. Haas et al. [63] revealed considerable sequence diversity across both intraspecies and interspecies RXLR and CRN effectors with high degree of expansion and pseudogene creation, based on comprehensive genome sequencing of several *Phytophthora* spp. Modular proteins with widely varied C termini and highly conserved N terminal domains are RXLRs and CRNs, respectively. Furthermore, the genomic context in which these effector genes are usually found is both repeat-rich and gene sparse. The dynamic nature and high rates of gene acquisition and loss seen for these effectors are partly explained by mobile elements in these repeated areas [63].

4. CONCLUSION

Phytophthora species are highly destructive plant pathogens, spreading rapidly and posing significant threats to agriculture and ecosystems. Interactions between Phytophthora and plants initiating defense responses in plants upon recognition of *Phytophthora* elicitors. Structural changes in plant cells, such as callose deposition and antimicrobial compound production, occur in response to *Phytophthora* attack. Cell wall appositions inhibit non-adapted *Phytophthora* pathogens. *Phytophthora* effectors suppress plant immunity, but resistant plants trigger ETI, leading to a hypersensitive response. Adapted *Phytophthora* species produce new effectors to evade plant defenses, showcasing a molecular arms race between both parties.

5. FUTURE THRUST

Plant defense against *Phytophthora* spp. is a complex, multilayered phenomenon where each defense layer is influenced by rapidly coevolving effectors, highlighting the importance of identifying new resistant genes to develop resistant plants. Beyond R gene mediated resistance, the discovery of host's S-factors targeted by multiple RXLR effectors suggests new avenues for *Phytophthora* resistant crop development. CRISPR/Cas-9 technology offers a promising approach to knock out negative immune regulators in plants. Research on *Phytophthora*-plant interactions, employing various omics approaches, aims to uncover novel defense components, potentially leading to broad-spectrum resistance. Non-race-specific genes can confer broad resistance, and exploring PAMP-initiated non-host resistance is crucial. Combining non-race-specific resistance sources with multiple R genes and S-factors could provide stable broad-spectrum resistance. Effector biology research is largely limited to specific pathosystems, necessitating broader research to comprehensively understand Phytophthora-plant interactions.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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