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**REVIEW ARTICLE**

# Host Plant Strategies to Combat Against Viruses Effector Proteins

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**Abstract:** Viruses are obligate parasites that exist in an inactive state until they enter the host body. Upon entry, viruses become active and start replicating by using the host cell machinery. All plant viruses can augment their transmission, thus powering their detrimental effects on the host plant. To diminish infection and diseases caused by viruses, the plant has a defence mechanism known as pathogenesis-related biochemicals, which are metabolites and proteins. Proteins that ultimately prevent pathogenic diseases are called R proteins. Several plant R genes (that confirm resistance) and avirulence protein (Avr) (pathogen Avr gene-encoded proteins [effector/elicitor proteins involved in pathogenicity]) molecules have been identified. The recognition of such a factor results in the plant defence mechanism. During plant viral infection, the replication and expression of a viral molecule lead to a series of a hypersensitive response (HR) and affect the host plant's immunity (pathogen-associated molecular pattern–triggered immunity and effector-triggered immunity). Avr protein renders the host RNA silencing mechanism and its innate immunity, chiefly known as silencing suppressors towards the plant defensive machinery. This is a strong reply to the plant defensive machinery by harmful plant viruses. In this review, we describe the plant pathogen resistance protein and how these proteins regulate host immunity during plant–virus interactions. Furthermore, we have discussed regarding ribosome-inactivating proteins, ubiquitin proteasome system, translation repression (nuclear shuttle protein interacting kinase 1), DNA methylation, dominant resistance genes, and autophagy-mediated protein degradation, which are crucial in antiviral defences.

**Keywords:** PAMPs (Pathogen Associated Molecular Patterns), plant defense, RNA silencing, PTGS (Post Transcriptional Gene Silencing), Avirulence Protein (AVR), innate immunity.

## 1. INTRODUCTION

Plants are constantly challenged by various phytopathogens [1] present in the environment they grow, and these phytopathogens exploit plants' biosynthetic and energy-producing proficiencies [2]. The host plant passively protects itself against harmful phytopathogens by using its waxy cuticular layers of the skin, which is the first line of defence from outside (Fig. **1**) [3]. Phytopathogens, including bacteria, fungi, insects, and nematodes, are responsible for causing biotic stress in plants, thereby interrupting the photosynthate formed by plants [4]. By contrast, viruses employ the replication machinery of the host plant for multiplication and movement [5]. Biotic stress in cash crop plants results from infection or disease these pythopathogens cause in the host plant for their growth and nutrient supply [6]. Although microbes grow and flourish on host plants, they affect plant growth and development as well as cause physiological changes in plants [7]. Plant microbiota are principally accumulated from external sources or inoculums, which can be in the harmful pathogenic form or beneficial endophytes (evade in pathogen transmission). This exerts a significant effect on plant health [8].

Most plant viruses possess RNA as their genome along with a coat protein called capsid, and a few viruses contain DNA [9]. Viral infections cause tremendous damage to crop plants, including chlorosis, necrosis, vein clearing, and wilting, thus affecting the physiology and morphology of plants [10, 11]. Once a virus enters the plant cell, it can easily infect nearby cells through cell junctions, namely plasmodesmata (Fig. **2**) [12, 13]. To tackle these phytopathogens, plants have two primary defence mechanisms: resistance (plant completely immunises itself from the infection) and tolerance (despite infection, production levels remain above the economic threshold) [14]. The plant defence mechanism exerts a negative effect on phytopathogens [15]. Therefore, host plants and their phytopathogens modulate the dynamics and genetic structure of each other's population [16]. With the course of evolution, plants have developed multilayered resistance responses to reduce the growth and spread of several disease-causing pathogens [17]. Therefore, new strategies to combat microbial plant diseases are exceedingly required to stop and reduce the transmission of microbial pathogens [18, 19].

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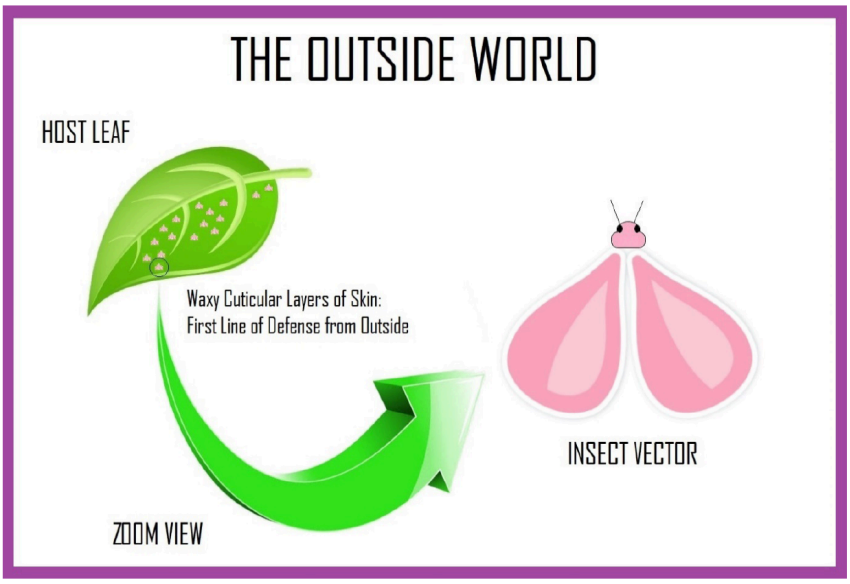


**Fig. (1).** Artwork of the outside world wherein the first encounter of the insect vector sucking saps from the host plant leaf. The host plant utilizes its passive protection against the harmful phytopathogens with the help of its waxy cuticular layers of skin: the first line of defense from outside. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

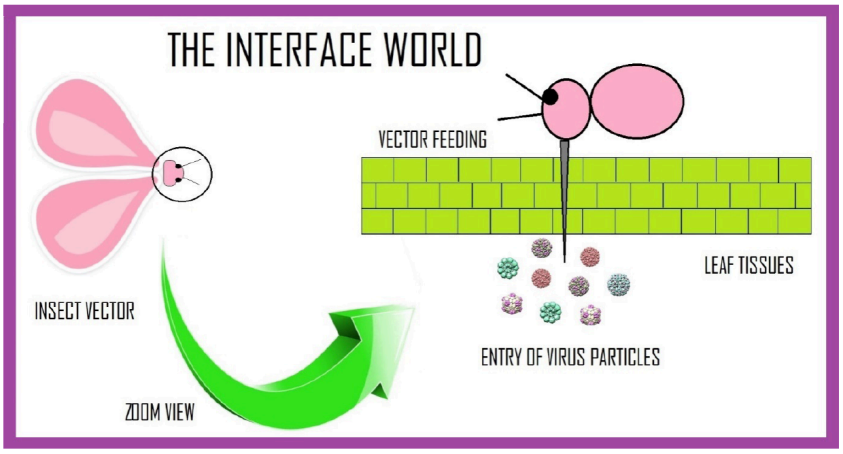


**Fig. (2).** The interface world diagram is showing the release/spreading/transmission of virus particles in the host plant caused by the insect vector through its stylet. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

An improved understanding of defence and counterdefence mechanisms employed between plants and pathogenic viruses is a prerequisite where both viruses and the host plant have developed specific strategies to improve their survival and propagation. Taking all this crosstalk between plant viruses and their hosts into account, in this review article, we discuss the latest paybacks and challenges of various viral resistance tactics and highlight plants' microRNA (miRNA) pathway.

## 2. MAJOR GROUP OF PLANT INFECTING VIRUSES AND VIROIDS

Plant viruses interact with different defence mechanisms of host plants (crops, weeds, and ornamentals). All plant viruses can augment their own transmission, thus increasing their detrimental effects on host plants. Plant viruses that cause viral infection stress in plants are double-stranded DNA (dsDNA) viruses, single-stranded (ss) DNA viruses, double-stranded RNA (dsRNA) virus, ss positive sense RNA viruses, and ss negative sense RNA viruses; these viruses consist of 16 families (Table **1**) and three orders. These three orders have been accepted thus far by the International Committee for Taxonomy of Viruses [20]. Of them, the largest group is the *Geminiviridae* family with nine genera and approximately 500 virus species [21, 22]. Viroids, which have free RNA molecules of a low molecular weight without any protein coat, are similar to viruses, and all viroids residing in plants for multiplication. Viroids are even smaller in size than viruses. To date, there are two known families of viroids, namely *Pospiviroidae* and *Avsunviroidae* [23, 24]. These two families together comprise approximately 30 known viroid species and cause diseases such as potato spindle tuber disease, apple fruit disease, hop stunt disease, tomato bunchy top disease, and chrysanthemum stunt disease. Mechanical damage, cross contamination, aphids, and contact of an infected leaf with healthy leaves are the modes of viroid transmission [25, 26].

**Table 1. Major plant infecting virus species.**

| S. No. | Family | Example | References |
|---|---|---|---|
| 1 | *Rhabdoviridae* | Lettuce necrotic yellows virus | [27] |
| 2 | *Bromoviridae* | Brome mosaic virus | [28] |
| 3 | *Sequiviridae* | Rice tungro spherical virus | [29] |
| 4 | *Bunyaviridae* | Tomato spotted wilt virus | [30] |
| 5 | *Tombusviridae* | Tomato bushy stunt virus | [31] |
| 6 | *Rheoviridae* | Fiji disease virus | [32] |
| 7 | *Closteroviridae* | Beet yellows virus | [33] |
| 8 | *Caulimoviridae* | Cauliflower mosaic virus | [34] |
| 9 | *Tymoviridae* | Turnip yellow mosaic virus | [35] |
| 10 | *Comoviridae* | Cowpea mosaic virus | [36] |
| 11 | *Circoviridae* | Banana bunchy top virus | [37] |
| 12 | *Geminiviridae* | Grapevine red blotch virus | [38] |
| 13 | *Partiviridae* | White clover crypto virus | [39] |
| 14 | *Flexiviridae* | Carnation latent virus | [40] |
| 15 | *Luteoviridae* | Barley yellow dwarf virus | [41] |
| 16 | *Potyviridae* | Barley yellow mosaic virus | [42] |

## 3. RESPONSES IN HOST PLANTS AGAINST PLANT VIRUS EFFECTOR PROTEINS

The active defence responses of the host against invading microbes are regulated by a complex signalling network mediated by gene-for-gene interactions [43]. This involves both the direct and indirect communication of pathogen avirulence (Avr) gene (effector/elicitor proteins involved in pathogenicity) [44] and its matching products (receptor proteins) of the plant resistance (R) gene (Fig. **3**). R proteins are similar and categorised on the basis of their structural domains and their localisation. R proteins intricated in protein–protein interactions consist of a leucine-rich repeat (LRR) domain [45-47]. R genes are divided into proteins encoding cytoplasmic LRRs (consisting of the nucleotide-binding site) and extracytoplasmic LRRs (consisting of the transmembrane region). Moreover, some of these R proteins contain a leucine zipper domain or a Toll/interleukin-1 receptor domain [48]. Apart from the aforementioned mechanism, there is the initiation of several defence allied genes along with pathogenesis-related genes [49]. Following the infection of some tissues, the uninfected parts of the host plant develop systemic acquired resistance [50]. This elaborate network of gene-for-gene interactions is usually understood as a receptor-ligand model, wherein the Avr protein binds to its corresponding resistance protein, finally switching on the plant defence mechanism [51].

Pathogen-associated molecular patterns (PAMPs) and microbe-associated molecular patterns are conserved in nature [52]. Once a phytopathogen launches an attack, releasing enzymes and proteins, several PAMPs are produced by plant cell receptors (pattern recognition receptors [PRRs]), activating their immunity. In response to this, pathogens further release effector proteins or Avr proteins to interfere with host receptors. In retort, the host plant battles pathogen invasion by producing effector-specific R proteins encoded by R genes, resulting in a hypersensitive reaction (HR) that makes the host plant resistant to the pest [53-55]. Examples of PAMPs are bacterial flagellins, lipopolysaccharides, fungal chitin, and oomycete heptaglucosides, and PAMPs are not yet recognised in plant viruses to date. In plants, RNA silencing, which is evolutionarily conserved in nature, is believed to be the first level of their defence against pathogen attack from within the plant [56].

The plant RNA silencing mechanism (also called as post-transcriptional gene silencing [PTGS]) [57] and its innate immunity (*i.e.* PAMP-triggered immunity [PTI] and effector-triggered Immunity [ETI]) control gene expressions and are generally sequence specific [58]; they can readily suppress or degrade foreign nucleic acids (viral DNAs/RNAs) (Fig. **3**) [59] and even transposons [60]. PTI and ETI involve rapid ion fluxes, antioxidative burst, and transcriptional reprogramming to handle viral infection [61, 62]. In addition to RNA silencing, ribosome-inactivating proteins (RIPs), ubiquitin proteasome system (UPS), translation repression (nuclear shuttle protein-interacting kinase 1), DNA methylation, dominant resistance genes, and autophagy-mediated protein degradation (AMPD) are crucial in antiviral defences [63-66].

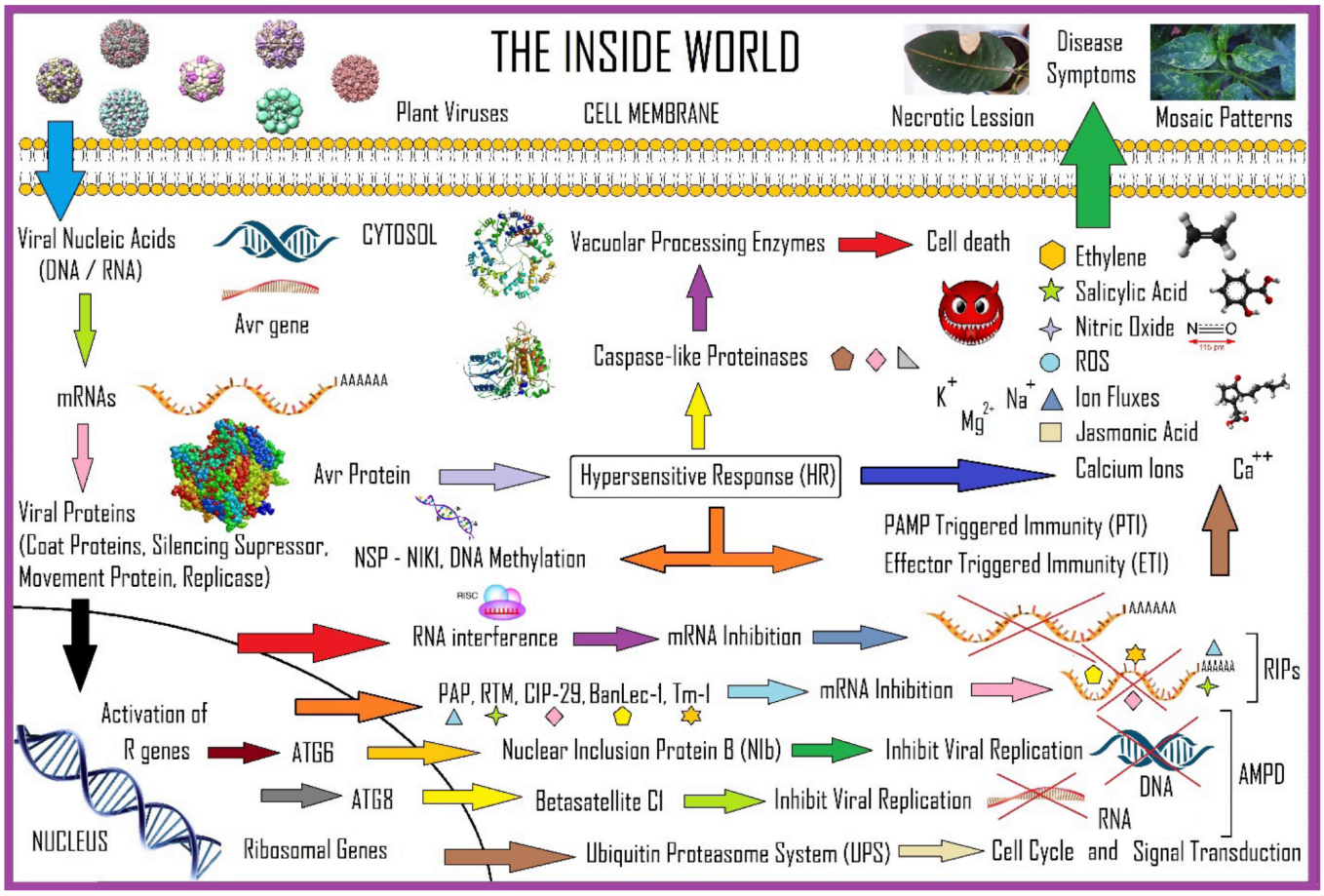


**Fig. (3).** Schematic overview of the inside world wherein plant R gene mediating resistance in host plant against the virus infections showing Hypersensitive Response (HR) resulted in typical symptoms of necrotic and mosaic patterns generated from the cell death. Several signalling molecules are induced during infection. Further plant antiviral pathways and viral counter-defenses are shown in the cytosol as a medium of plant–virus interactions. Wherein the viruses encode proteins to execute all parts of the infection cycle and the host factors target viral proteins and nucleic acids to restrict virus infection. Mechanism highlighted in the artwork was RNA silencing, Ribosome-inactivating proteins (RIPs), Ubiquitin Proteasome System (UPS), Translation Repression [Nuclear Shuttle Protein (NSP) Interacting Kinase 1 (NIK1)], DNA Methylation, Dominant Resistance genes and Autophagy Mediated Protein Degradation (AMPD). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

### 3.1. NB–LRR Proteins Hydrolysing Viral Genome

Initially, a pathogen is recognised by the extracellular surface PRR, followed by a series of kinases that are activated upon activation of PTIs (*e.g.* somatic embryogenesis receptor-like kinase and mitogen-activated protein kinases) [67-69]. However, viral PAMPs and plants' PRR mechanism are still under research. Many of the identified R gene products (*i.e.* R proteins) are of the nature of nucleotide-binding–LRR (NB–LRR) proteins and constitute a subgroup under the STAND (signal transduction ATPases with numerous domains) family [70, 71]. NBS-LRR proteins are some of the largest proteins known in plants, ranging from approximately 860 to 1900 amino acids. They have at least four distinct domains joined by linker regions: a variable amino-terminal domain, the NBS domain, the LRR region, and variable carboxy-terminal domains. NB–LRR proteins stipulate gene-for-gene resistance against phytopathogens and cooperatively establish a complete pathogen detection system. Multidomain NB–LRR proteins can bind to the foreign viral genome (DNA/RNA) and hydrolyse them into monomeric forms [72, 73]. One particular Avr molecule might correspond to one specific or matching R protein. Another essential thing to consider is that upon activation, R proteins trigger programmed cell death, and its directive by the host cell is quite essential [74]. This autoinhibition occurs due to intramolecular interactions among various domains necessary to keep R proteins inactive under plants' normal conditions (uninfected) [75].

### 3.2. What's Happening in Hypersensitive Response (HR)

Approximately 500 species of plant pathogenic viruses that are responsible for various diseases are considered an intracellular parasite [76]. Because viruses encode relatively few proteins, such as coat proteins, replication proteins, P25 protein, RNA-dependent RNA polymerase, helicase, P3 protein, HcPro proteins, NIa protease, NSs protein, viral protein genome-linked, and virus movement proteins, all are known to assist as Avr factors in different plant/viral systems [77]. The basic noticeable feature of gene-for-gene mediated resistance is the development of an HR by the plant against phytopathogens [78] wherein necrotic lesions or ringspots are developed at the location of infection on leaves, stems,

and fruits, confining the phytopathogen within it and thus protecting noninfected tissues (Fig. **3**) [79]. Furthermore, during an HR, modifications occur in the plant cell wall structure, such as an increase in the calcium ion concentration; an oxidative burst (superoxide and nitric oxide); and upsurges in endogenous salicylic acid, jasmonic acid, and hydrogen peroxide levels [80, 81]. In addition, during an HR, numerous caspase-like proteinases, such as vacuolar-processing enzymes, are triggered, acting as effectors of cell death [82].

### 3.3. Plant Protecting RIPs, AMPD and UPS

RIPs are scattered all over the plant body and can inactivate viral proteins. One such example is *Phytolacca americana* (pokeweed) whose protein possesses antiviral activity (*i.e*. the pokeweed antiviral protein). Several examples have been well documented in suppressing viral activities, such as those of cucumber mosaic virus, potato virus X (PVX), and potato virus Y [83, 84]. The family of dominant resistance genes generally encodes for the lectin family of proteins, which confirm strong resistance against plant viruses. For example, Arabidopsis-restricted Tev movement 1 provides resistance against potyviruses, CIP-29 from *Cyamopsis tetragonoloba* (L.) suppresses Sunn-hemp mosaic virus, BanLec-1 from *Musa paradisiacal* inhibits tobacco mosaic virus, and Tm-1 from tomato provides protection against tomato mosaic virus. Likewise, tobacco plant N protein recognises and suppresses TMV replicase and potato plant resistance proteins, Rx, Rx2, and Green Peach Aphid 2, help in the recognition of PVX coat protein and confirms resistance against the same. Even Arabidopsis jacalin-type lectin, JAX1, confers resistance against multiple potexviruses (PVX, PLAMV, white clover mosaic virus, and asparagus virus 3) [85-88]. Similarly, in case of autophagy-mediated protein degradation, several genes have been identified that suppress virus replication, such as autophagy-related gene 6, which interacts with the nuclear inclusion protein B of potyviruses, and ATG8 that interacts with the C1 of cotton leaf curl Multan virus betasatellite to inhibit its replication [89, 90]. UPS regulates plant cellular activities such as the cell cycle, transcription, and signal transduction. UPS with its various enzyme complexes are employed by plants to defend against pathogenic viruses (Fig. **3**) such as tobacco mosaic virus, turnip yellow mosaic virus, and tomato yellow leaf curl Sardinia virus [91].

### 3.4. Host Plant PTGS/RNAi Shield Against Viruses

According to optimal defence theory, new plant leaves serve as a basis of healthier nutrition to pathogenic attack compared with older leaves because the photosynthetic apparatus in new leaves is intact. Hence, the young leaves of host plants exhibit higher biotic stress responses compared with old leaves [92]. When plants are under multiple stresses, they become more tolerant or resistant to different stresses, which is known as cross-tolerance that makes host plants adapt rapidly to a changing environment [93]. PTGS in plants is an RNA-mediated virus resistance technique used to silence the expression of one or more pathogenic virulence genes [94]. In this technique, resistance depends on transcribed RNA. Plant RNA silencing was first recognised as an antiviral mechanism that protected plants against RNA viruses or the random integration of transposable elements [95]. With time, it was revealed that several miRNA genes are conserved evolutionarily, and their primary function is to cleave complementary sequence miRNAs [96]. Apart from these microRNAs, there are trans-acting small interfering RNAs (ta-siRNAs), natural-antisense RNAs, repeat-associated siRNAs, viral siRNAs (vsiRNAs), and virus-activated siRNAs. Each of these has its own specificity in terms of origin, biosynthesis, or mode of action. However, they all share some common features. Either encoded by the plant genome or originated from a viral pathogen, the generation of these RNAs involves certain dedicated enzymatic activities. dsRNA produced by pathogenic viruses activates the RNAi mechanism, which is acknowledged and processed into short 20-24 nucleotides by the host cell Type III endoribonucleases (DICER-like proteins) (Fig. **3**). Fragmented nucleotides, the so-called RNA duplexes, are integrated into ARGONAUTE (AGO) proteins, finally forming the RNA-induced silencing complex (RISC). The RISC complex then tends to recognise and cleaves the virus homologous nucleotide, thus suppressing viral protein translation [97, 98].

### 3.5. Studies Enabling PTGS/RNAi Resistance

This evidence was based on demonstrations that were related to the involvement of short miRNA molecules in RNA silencing in plants. Examples include the silencing mechanism used against tomato leaf curl virus, PVX, Citrus tristeza virus, and many more [99, 100]. This natural method of showing tolerance to viruses and viroids is known as the PTGS or RNAi mechanism. Excess hormone production in crop plants renders the multiplication of viruses; for example, suppression of tobacco necrosis virus (TNV) was observed in the cytokinin-overproducing transgenic tobacco line (CTKm), delaying the senescence of CTKm plants [101]. This also results in the reduction of virus disease symptoms, and a low titre of coat protein was found in host cells. In addition, less production of ethylene, ethane, and hydrogen peroxide as well as a low level of lipid peroxidation were observed. Hence, the host plant becomes quite efficient in reactive oxygen species (ROS)-scavenging ability, thus making the plant tolerant to TNV [102]. The expression of animal antiapoptotic genes, bcl-xL and ced-9, into tomato plants enhanced plant survival under biotic stress against the D satellite RNA (satRNA) [103]. The same approaches are observed in viroids. In addition to this, the overexpression of host proteins reduces viroid replication through AGO proteins and Dicer-Like endonucleases [104-106].

## 4. VIRUSES RETORTS FOR ITS SURVIVAL

Pathogenic viruses have a deficiency of proofreading its genome, and this results in a considerably high rate of mutations in its genetic material. The host immune response is activated upon recognition of a specific miniature sequence present in viral AVR proteins by R proteins (Fig. **3**). Mutated viruses easily escape from the host immune response, and this escaping is known as resistance breakdown [107, 108]. Likewise, these viruses also hinder the plant RNAi mechanism, PTI signalling, host ubiquitination pathways, host ROS production, and SA accumulation and suppress host autophagy pathways through its various encoded proteins [109]. In

the case of RNA viruses (in the majority of plant viruses), the replication process comprises a step where dsRNA is generated, which can trigger the process against the viral genome. For DNA viruses, overlapping bidirectional read-through transcripts or highly structured viral transcripts may play the triggering role. This never-ending battle between hosts and parasite viruses has resulted in the development of mechanisms against this potent plant defence route. Plant viruses hinder the RNAi pathway either by regulating endogenous miRNA expression or suppressing endogenous gene expression through vsiRNAs. For example, the viral suppressor of RNA silencing (p19) of the cymbidium ringspot virus can downregulate the transcripts of AGO proteins [110].

## 5. GROUND REALITY FOR FARMERS

Self-defence mechanisms employed by plants against viruses are much more complex than those against other phytopathogens such as fungi and bacteria [111]. This holds true because in comparison with fungi and bacteria, viruses reside as an intracellular parasite in host plants, wherein its genetic material is directly in access to acquire plant intracellular factors for its own well-being [112]. A true battle situation occurs in this face to face interaction between the two, where the plant attempts to evolve itself to develop new defence mechanisms to launch a stronger attack against pathogenic viruses [113]. Plant viruses benefit themselves in this face-off by identifying lacunae to escape or survive by using defence mechanisms [114]. CRISPR/cas9 is the most recently developed genome-editing tool with a range of genome-editing possibilities. CRISPR/Cas9 has been used to induce resistance in Arabidopsis to make it resistant against turnip mosaic virus by introducing a mutation on the elF (iso) 4E locus [115]. Similarly, CRISPR/cas9 was used to develop resistance in cucumber against viral diseases, including cucumber vein yellowing virus, zucchini yellow mosaic virus, and papaya ring spot virus, by modifying its elF4E gene [116-118]. Developing virus-resistant varieties of plants is the best step for managing diseases because it is the cheapest and effective approach to reduce economic yield losses caused by plant viruses [119]. Virus resistance can be specific or nonspecific [120]. The natural plant immune system contains dominant and recessive resistance genes [121]. Knowledge of these genes helps in implementing an appropriate preventive measure against viruses. The development of biotechnological approaches, such as the identification of viruses, control measures through RNA interference, and CRISPR-Cas9 [122], may not directly help farmers, but they can be advised to use comprehensive, integrated strategies for viral disease management [123, 124].

## CONCLUSION AND TAKE AWAY

Plant virus effector proteins play a crucial and dynamic role in understanding the mechanism of plant–microbe interactions. There is a practical intersection between R gene-mediated resistance and the RNA silencing mechanism. It still remains unclear how plant defence mechanisms, including pathogenesis-related genes, hypersensitive responses, systemic acquired resistance, PAMPs, RNA silencing, PTI, and ETI, act as an antiviral defence to manipulate resistance in plants. It will be quite interesting to study how host and virus influence each other in confirming disease resistance mechanisms in plants. Plant viruses have developed a variety of mechanisms to overcome the regulatory machinery of the host and interact tightly with the host protein synthesis machinery such that host genes can function as recessive resistance genes. Understanding virus effectors (Avr factor) and host targets (R proteins) and their mode of action can help to define the evolutionary pressure acting upon host–virus interactions. By discussing different plant effector proteins in this article, we hope to provide new directions to solve the mystery of host–virus interactions. The eventual goal of plant–virus interaction studies is to create sustainable virus resistance stratagems, implement better management practices, perform early diagnosis of viral diseases, and develop virus-resistant crops ethically for ensuring better food safety of the mounting human population in the current century.

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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