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REVIEW ARTICLE

Advances in understanding plant-pathogen interactions: insights from tomato as a model system

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Abstract
The impact of plant diseases coupled with climate change on agriculture worldwide cannot be overemphasized from negative effects on crop yield as well as economy to food insecurity. The model plants are essential for understanding the intricacies of plant-pathogen interactions. One of such plants is the tomato (*Solanum lycopersicum* L.). Researchers hope to increase tomato productivity and boost its resilience to pathogen attacks by utilizing OMICS and biotechnological methods. With an emphasis on tomato viral infections, this review summarizes significant discoveries and developments from earlier research. The analysis elucidates ongoing efforts to advance plant pathology by exploring the implications for sustainability and tomato production.

Keywords Arms race · *Solanum lycopersicum* · Resistance · Susceptibility · Viruses · Food security

Introduction

Tomato is an economically important vegetable being cultivated globally. It contains the most substantial dietary lycopene, flavonoids, β-carotene, hydroxy-cinnamic acid derivatives and vitamin C. It possesses antioxidant, anti-inflammatory and anti-thrombotic activities. Moreover, it offers superior bioavailability after cooking or processing and helps to reduce disease risks. However, various pathogens and climatic changes adversely affect its quality and yield [1–7].

Plant diseases significantly impact global agriculture, affecting crop yield, food security, and economies. To combat these diseases, plants, including tomatoes, have developed different defence mechanisms in response to pathogen attacks causing infectious diseases. [8–10]. Moreover, scientists have turned to model plants that offer insights into the complexities of plant-pathogen interactions. One such model, the tomato (*Solanum lycopersicum* L.), has emerged as a valuable asset in advancing our understanding of these interactions. Tomatoes are not just a staple in our diets; they are a crucial resource for researchers. This red, juicy fruit boasts several characteristics that make it an ideal plant for studying plant-pathogen interactions. The experimental tractability of *S. lycoper*sicum in laboratory settings allows scientists to investigate various plant pathogens and their strategies for breaching plant defences [11–14]. Additionally, the tomato's vast genetic diversity and the wealth of available genomic information as well as tomato pathogen diversity, facilitate research to unravel the genetic and molecular basis of disease resistance and susceptibility and reiterate its important position in the pathogen system [3, 11, 15, 16]. These pathogens have co-evolved with their hosts, triggering intricate molecular antagonism between them, where plants deploy defence mechanisms to repel disease-causing microbes, while the pathogens including viruses in turn employ strategies to subvert these defences [17, 18]. Viruses are obligate intracellular microorganisms that usually remain inactive until they find their way into the hosts [19, 20]. They alter the cellular processes of their hosts to their advantage, thereby ensuring their successful reproduction. Due to their miniature sizes coupled with their relatively limited coding ability, the viruses produce proteins with multifunctional characteristics [19].

The advent of cutting-edge technologies, collectively referred to as OMICS approaches (such as transcriptomics, genomics, proteomics and metabolomics), has

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revolutionized the study of plant-pathogen interactions [21–24]. These techniques allow researchers to dissect the molecular interaction that occurs when crop plants are infected by disease-causing microbes, providing critical insights into the dynamic nature of these interactions [27]. Furthermore, biotechnological interventions, such as genome editing and genetic engineering, promise to enhance disease resistance in tomato crops [26–29]. However, the utilization of these powerful tools raises ethical and regulatory considerations that need careful examination [30–33].

Emerging challenges from new pathogens and changing environmental conditions directly affect agricultural sustainability and food production [34–37]. As such, this paper explores potential research directions and technological advancements that will shape our understanding of plant-pathogen interactions using tomatoes as a model system [26]. By carefully going through recent research findings and taking cognizant of the important roles played by tomato plants, this review aims to highlight some of the findings related to plant-pathogen interactions.

Plant-pathogen interaction

A cascade of events, such as pathogen attacks, is involved in plants' reaction to biotic stress. The viral small interference RNAs (vsiRNAs) target plant host genes that are associated with defence pathways [38, 39]. Firstly, the signal input from the pathogen is recognised by the appropriate receptor (putative Resistance genes (R-genes)) on the cell surface of the host plant, which subsequently triggers the defence mechanism. Afterwards, signal transmission induces the production of defence molecules such as heat shock proteins (HSPs), pathogenesis-related (PR) proteins and secondary metabolites in the cell [38, 40]. The compatible interaction between pathogens and host plants leads to the multiplication of pathogens and their spread. It thereby leads to infection and the secretion of effectors by some pathogens enhances their virulence [1, 41].

Moreover, compatibility hinges on favourable environmental conditions. Besides, viral infection establishment depends on the availability of host factors which are genetically controlled and are important in the replication and movement of the viral genome, as well as the balance between the plant defence mechanism and its suppression by the virus [16, 41]. Host factors possess either antiviral or proviral activities; the host factor's proviral activity leads to host plant susceptibility to viral attack, while the presence of anti-viral or absence of proviral activity in the host plants gives rise to mild infection or complete absence of infection [16]. Moreover, the incompatible relationship between the host and its pathogen results in plant resistance against the pathogen. [40, 41]. Plant-pathogen interaction can be assessed through two traits; plant-related and pathogen-related traits. The former evaluates the effect of the disease on the plant and to what extent it can tolerate the pathogen's presence while the latter assesses the pathogen's life cycle and the host's ability to affect its dynamics. The heritability of the evaluated traits determines the reliability of the assay employed, provided the pathogens do not evolve [41].

Pathogen-associated molecular pattern (PAMP), is a conserved and unique molecular pattern which is identifiable by the plant membrane pattern recognition receptors (PRRs) (Fig. 1) [42] at the cell surface, which then triggers signalling cascades that lead to PAMP-triggered immunity (PTI), a basic immune response [1, 39, 40]. In the quest to further hijack the host plant completely, an arms race between the host and pathogens leads to the evolution of a novel mechanism of defence and counter-defence that involves a hormone-mediated signalling pathway [15, 40, 43]. Plant pathogens secrete effector proteins which enhance their virulence. Effector proteins are non-structural proteins encoded by either small RNA (sRNA) segments or messenger RNA (mRNA) (NSs or NSm). This action prompts the host plant cell to activate another level of defence response called effector-triggered immunity (ETI), and hypersensitive cell death response (HR) will be produced. The HR prevents further spreading of the pathogen in the host, and it can be physically recognized via localized necroses at the point of pathogen attack on the plants (Fig. 2) [41, 44].

NSs were said to be associated with hormone receptors and these proteins hamper the activity of the hormone-signalling pathways associated with it. NSs indirectly interact with hormone receptors; instead, they bind to a protein known as TCP21, that interacts with these receptors which in turn represses their signalling activities. This interaction prevents the degradation of proteins involved in the suppression of the hormone-signalling responsive genes' expression and thereby, enables virus infection in the plants. Conversely, the host plant counterattacks by evolving a resistance (R) gene that recognizes this interference and thereby triggers defence [45]. Additionally, in Capsicum-infecting Begomoviruses (CIBs), epigenetic modifications of histones associated with minichromosomal structure are very crucial in the molecular arms race between viruses and their hosts [46]. Specific effectors from different pathogens are identified by nucleotide-binding site leucine-rich repeat (NBS-LRR) protein receptors [1, 39]. Plant NBS-LRR protein receptors can be divided into two groups, namely: Coiled-coil NBS-LRR (CC-NBS-NRR) and Toll/interleukin-1 Receptor (TiR-NBS-LRR) receptors [39, 41]. The activation of PTI and ETI leads to a buildup of some plant hormones such as salicylic acid (SA), jasmonic acid (JA), ethylene and abscisic acid (ABA) and SA stimulates transcription of a number of R-genes [39].

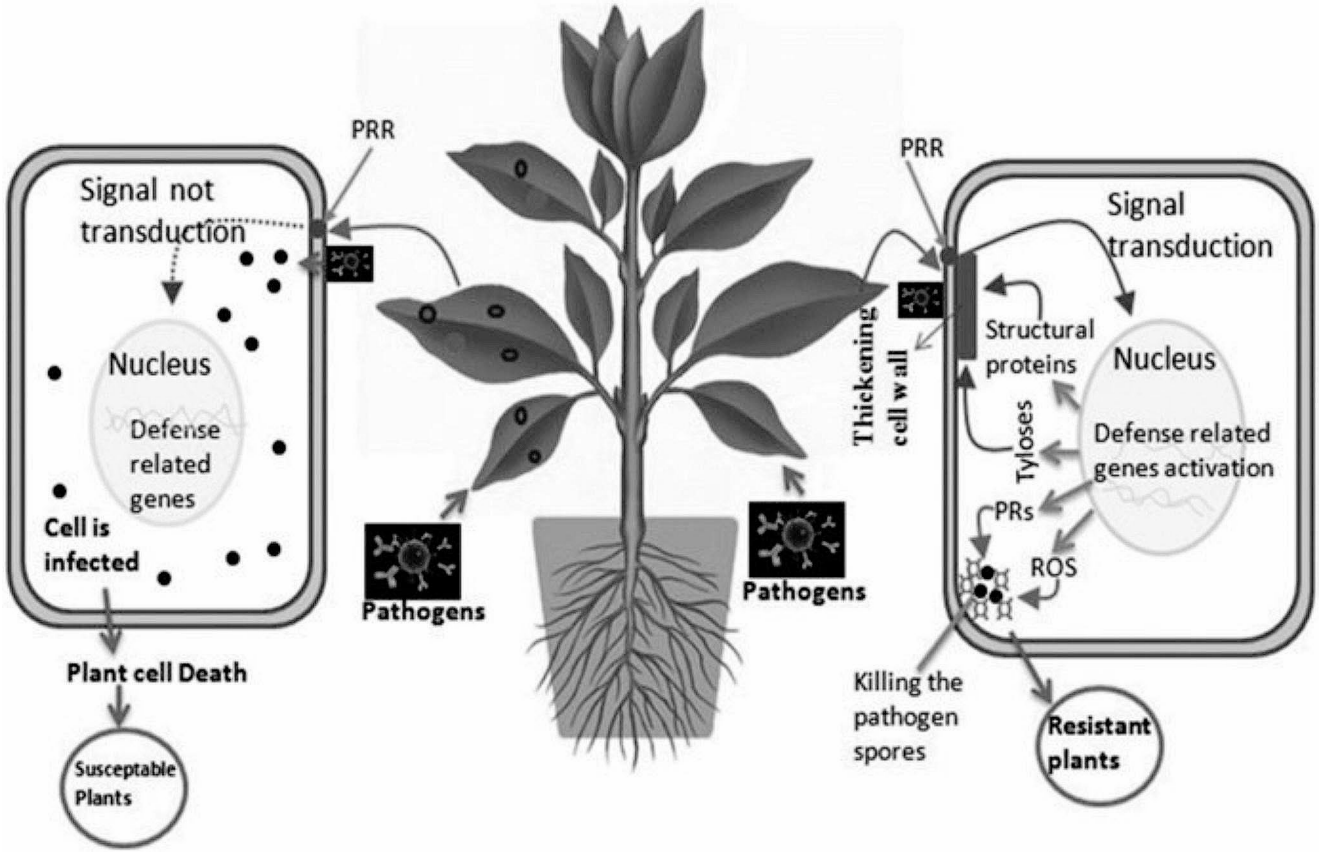

Fig. 1 Plant resistance mechanism against pathogens. (Diagram adapted from Md Abdul et al. 2016 cited in Poonam et al. 2017)

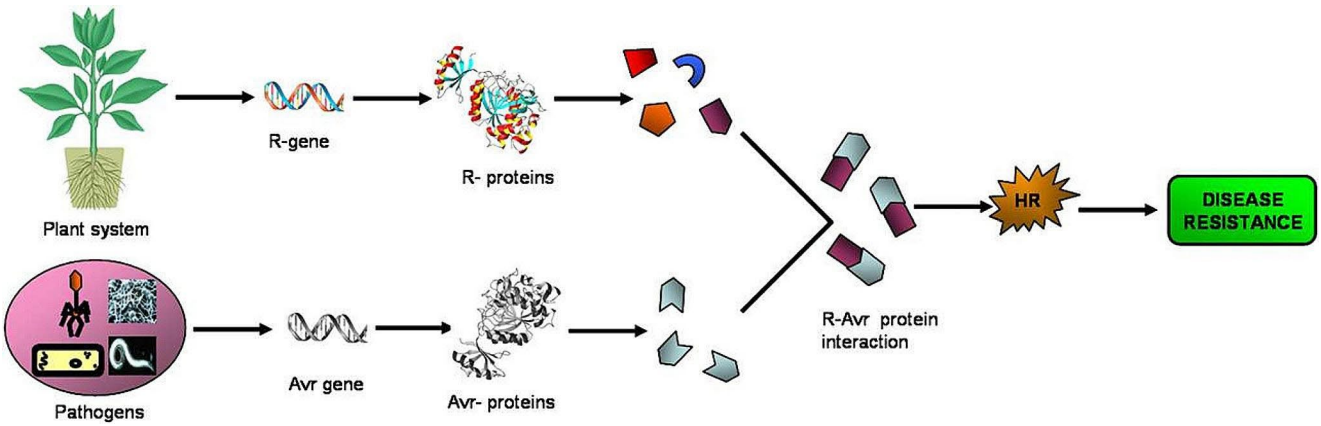

Fig. 2 The arms race between the host plant R-proteins (R-genes) and the avirulence protein (AvrPro) (Diagram adapted from Gururania et al. 2012)

Effector proteins

Plant pathogens secrete effector molecules into the host plant thereby undermining the plant's cellular immune responses to infections through a process known as effector-targeted pathway (ETP) [47]. Effectors play a major role in plant-pathogen interaction and understanding their roles in plant-pathogen interaction will give an insight into how they can be manipulated to enhance plant resistance to the viruses; they are hypothesized to be important in identifying R-genes [41, 47] and subsequently, elucidating the major players in the plant immunity pathways [47]. Many host plant defence pathways such as natural immunity, RNA silencing, transcription, vesicle trafficking and cell signalling are targeted by effector proteins. Many of these are amassed on conserved proteolytic degradation pathways like autophagy

and the Ubiquitin-proteasome system (UPS). These constitute important aspects of the plant defence system which determine the outcome of plant-pathogen interaction [47].

These effector proteins are encoded by avirulence (Avr) genes. As the pathogens attack the host plants, they introduce effector proteins also known as Avr proteins (AvrPro) directly into the plant cells at the beginning of infection. The effectors subsequently alter the physiological condition of the host to the advantage of the pathogens or suppress the activation of the host plant defence mechanisms [44]. Effector proteins released into host plant cells by the pathogen trigger a defence mechanism known as R-gene-mediated pathogen resistance [44]. Each R-gene product corresponds to an avirulence factor (Avr) encoded by the virus (Fig. 2) [44, 48]. This resistance is stimulated by the two above-mentioned factors while the modification of any of them or their absence results in susceptibility to pathogens [41]. In a different model, the plant host factor known as Pto protein kinase is modified when targeted by the pathogen's AvrPro. The R-gene Prf identifies this modified molecule and subsequently stimulates a series of resistant events [41]. For instance, *Capsicum annuum* L. and C. *chinenses* Jacq. (resistance cultivars) possesses the *Tsw* gene that recognizes NSs effector protein from tomato spotted wilt virus (TSWV) (*Orthotospovirus tomatomaculae*), thereby inducing defence against the virus [45, 49]. Therefore, the host plants employ RNA interference (RNAi) mechanisms coupled with an inherent plant immunity to prevent TSWV attack [39]. In view of the above, the phenotyping of HR provides new tools that can be employed in screening the gene pool of variability, through the specific recognition between R- and Avr proteins [48].

Effector proteins can be classified into three main groups, namely: degraders, suppressors and stabilizers. Viral effectors like β-C1, TYMVpro, and p25 from cotton leaf curl Multan virus (CLCuMuV) (*Begomovirus gossypimultanense*), turnip yellow mosaic virus (TYMV) (*Tymovirus brassicae*) and beet necrotic yellow vein virus (BNYVV) respectively are examples of stabilizes; the stabilizers directly or indirectly prevent the degradation of target proteins thereby promote diseases while HCPRO from potyviruses was categorized as suppressor which acts as RNA silencing suppressor [47]. Nla-Pro associated with turnip mosaic virus (TuMV) (*Potyvirus rapae*) and potato virus Y (PVY) (*Potyvirus yituberosi*) is likely to be a degrader [50] and some of the viral effectors play a dual role [47]. Moreover, some effector proteins from viral pathogens for example γb, P4 protein and HcPro from barley stripe mosaic virus (BSMV), cauliflower mosaic virus (CaMV) and TuMV respectively target autophagy pathway and they are in turn targeted by the host plant cells in a counterattack [47].

Host plant resistance and susceptibility

Numerous plant diseases are caused by viruses, which negatively affect plant quality and yield and the tomato plants are not left out [2]. The viruses are popular with hijacking and utilizing the genome of their host plants to their advantage and there are no curative measures for viral diseases except for cultural practices such as prophylactic methods, the use of pesticides/insecticides, as well as the adoption of genetic resistance to reduce the damage resulting from viral infection [2, 3, 5]. Owing to the non-availability of antiviral products, an important and environmentally friendly aspect of the sustainable disease management system is the identification/development of host resistance against pathogens from genetic resources mostly selected from landraces and wild relatives. However, in the course of crop domestication and plant breeding, many resistance genes that are mostly linked to undesirable characters have been lost [5, 38, 39, 41, 51–54]. Since it is difficult to eradicate tomato viruses due to their high genetic diversity because of the high occurrence of mutation in these viral genetic materials coupled with their fast-spreading nature, [5, 48], it will be important to identify and remove the non-redundant proteins in the host according to the biological characteristics of the viruses coupled with RNAi technology as another alternative to combat tomato viruses [55]. Moreover, proper weed management needs to be taken into consideration as some weeds including members of the family Solanaceae to which tomato belongs, serve as reservoirs for tomato viruses [56–60].

Three criteria are employed to measure host plant resistance: durability, efficacy and spectrum of resistance. A simple biological assay under artificial conditions is adopted to assess the host plant's resistance to diseases [41]. Effector proteins manipulate or alter the host cellular function by either overpowering the plant defence mechanism or imitating the avirulent factor when it is identified by resistance protein [41]. However, from an array of pathogen avirulent genes, most conserved effectors can be identified, manipulated and employed to develop alternative and efficient R-genes against pathogens [41]. Resistance can be grouped into qualitative/simple and quantitative/complex resistance. In simple resistance, the susceptible progenies are clearly distinguished from resistant ones. Qualitative resistance is mostly involved in plant defence strategies against biotrophic pathogens. R-genes play vital roles in the recognition and stimulation of defence against pathogens and the resistant alleles involved are generally dominant alleles while the loss-of-function in S-genes will lead to plant resistance against pathogen attack; however, this type of resistance remains a recessive form of resistance [41, 61].

It should be noted that S-genes are primarily important in plant biological processes including plant development and their modification may have undesirable effects on plant production [40, 41, 61]. On the other hand, quantitative resistance shows an extensive range of responses to infection from the most resistant plant to the most susceptible one. It is a polygenic trait with minor effects and it can be environmentally influenced; it has the prospect of conferring broad-spectrum and long-lasting resistance on the host plant against pathogens [41, 61].

Tomato yellow leaf curl virus (TYLCV) (*Begomovirus coheni*) is from the Geminiviridae family and it causes stunted growth, leaf curling, leaf yellowing and flower abscission with nearly no yield on infecting tomato plants. It is spread by whitefly (*Bemisia tabaci*) [2, 38, 62]. Some genes were identified to be related to TYLCV resistance pathways, which include cell wall formation and reorganization, ethylene response, salicylic acid biosynthesis, tryptophan/nicotinate, phenylpropanoid, urea/polyamine pathways [63, 64], transcription factors (TFs), defence response, metabolite synthesis and ubiquitination [38]. Resistant genes against TYLCV in tomato plants have been identified from its wild relatives (*Solanum peruvianum* L., *S. pennellii* Correll, *S. cheesmaniae* (L. Riley) Fosberg, *S. pimpinellifolium* L., *S. chilense* (Dunal) Reiche, and *S. habrochaites* Knapp& Spooner). So far, six Ty resistance genes (Ty-1, Ty-2, Ty-3, Ty-4, Ty-5 and Ty-6) were identified, and mapped onto different chromosomes and they are inherited independently [3, 5, 62, 65, 66]. It was suggested that Ty-1 boosts an antiviral TGS response as it changes the antiviral small interfering RNA (siRNA) profile [67]. The interaction among the Ty-resistant genes can give rise to hybrid plants with better resistance ability in comparison with their parent lines. In a study, it was revealed that tomato cultivars with Ty-1/Ty-3 and Ty-2 combination gave the highest level of resistance against begomoviruses [5, 68].

Moreover, molecular markers corresponding to each of the genes were developed and three of them were successfully cloned and characterized [62]. Through Marker-assisted selection (MAS), these resistant genes were effectively incorporated into commercial cultivars in India via introgression [62]. MAS is another tool that is being employed in modern breeding in recent times because it improves selection accuracy, reduces breeding costs and not environmentally influenced, and helps in the pyramid cation process of resistant genes as the conventional plant breeding is time-consuming, especially in case of polygenic traits and is less precise [62, 69]. Moreover, MAS enables the aggregation of various R-genes that will enhance stability and prolonged resistance [39]. However, pathogenic viruses are characterized by a deficiency in proofreading their genome which consequently leads to a high mutation rate of their genetic materials. Therefore, viruses with mutated genetic material usually suppress the host plant's defence mechanism and this phenomenon is known as resistance breakdown [20]. The incomplete or complete collapse of resistance against TYLCV in tomato plants has also been documented especially for Ty-1 and Ty-2 due to mutation and recombination as a result of mixed infection and therefore, there is a need to continuously search for novel R-genes from the tomato gene pool of variability [41, 62, 65].

Tomato spotted wilt virus (TSWV) (*Orthotospovirus tomatomaculae*), a member of the Tospoviridae family is among the topmost destructive tomato viral diseases globally, causes stunted growth with chlorotic or necrotic spots on leaves and fruits, leaf rolling and rings on leaves and stems. Its main carrier is Western flower thrips (*Frankliniella occidentalis*) and it invades the host plant through mechanical inoculation. TSWV infected its vector at the larval stage [3, 38, 39, 62, 70]. In some cultivars/varieties, genes associated with TSWV resistance were identified. These genes have a connection with NBS-LRR proteins, TFs, protein kinases, host defence, phytohormone signalling, cell wall, photosynthesis, gene silencing and miRNA targets [38]. The largest family of R-gene encodes NBS-LLR, and the organization of NBS-LRRs in the cluster is involved in the evolution of R-genes through intra- and inter-genic recombination as well as sequence exchanges [41].

Additionally, some natural resistant genes (*Sw*) were identified in some tomato cultivated lines and some of its wild relatives such as *Lycopersicon peruvianum* Mill., (Synonymy *Solanum peruvianum*), *L. pimpinellifolium* Mill. (Synonymy *S. pimpinellifolium*). These include: *Sw1a*, *Sw-1b*, *Sw-2*, *Sw-3*, *Sw-4*, *Sw-5*, *Sw-6*, and *Sw-7*; *sw-2*, *sw-3*, *sw-4* are usually in recessive forms [2, 3, 41, 69, 70]. *Sw-5* can reduce and/or control the virus movement. There was speculation that TSWV-RdRp is being degraded by a corresponding action in the plant defence pathway or probably the *Sw-5*'s function stems from the absence of a TSWV protective system [71]. Early identification of NSm protein by Sw-5 protein likely activates the programmed cell death (PCD) in the immune response pathway [71]. Alternatively, a silencing interference network might have rapidly targeted RdRp leading to the synthesis of a high number of vsiRNAs complementary to the NSs. In a counterattack, the synthesized vsiRNAs could have been used to the advantage of the virus by targeting the host genes resulting in a viral infection cycle [71].

Over time, resistance induced by *Sw-5* as well as other R-genes to other viral diseases is being compromised due to the emergence of new isolates and constant mutation. New viral emergence is driven by plant viral genetic variability and recombination, pseudo-recombination, the acquisition of extra genomic components, changes in

climatic conditions resulting in enabling environments for viruses, exchange of plant materials, changes in agricultural practices, trades and ease of human movement across the globe [2, 5, 41, 72–74]. Moreover, mixed viral infection allows intra-species and inter-species recombinations which encourages synergism that leads to the development of new viral isolates and the breakdown of host plant resistance against different viruses as shown in a mixed reaction that involved TYLCV and tomato chlorosis virus (ToCV) (*Crinivirus tomatichlorosis*) which is more severe compared to single infection. Similarly, a co-infection involving TYLCV and tomato yellow leaf curl Sardinia virus (TYLCSaV) (*Begomovirus solanumflavusardiniaense*), automatically resulted in the recombination of the two viral genomes giving rise to an emergence of new viral isolates (TYLCV/TYLCSaV recombinant (LSRec)) in southern Morrocco. This recombinant then replaced the parental viruses as it possesses better fitness when compared with its parental viruses and was stimulated by beneficial intra-genomic interaction [46, 75–78]. The recent effort towards the development of lasting and durable resistance against pathogen attack involves the employment of combinations of R-genes at the molecular level or in the field to prevent the evolution of pathogen population [41] and a tomato resistant line against TYLCV, tomato torrado virus (ToTV) (*Torradovirus lycopersici*), and tomato marchitez virus (ToMarV) (*Torradovirus marchitezum*) has successfully been developed [5].

A newly discovered gene, *Sw-7* has been demonstrated to confer resistance on some tomato lines against an array of TSWV [39, 72]. *Sw-7* was proven to engender resistance against a large variety of TSWV strains and it was established that PR-5 plays a crucial role in Sw-7 resistance. Its overexpression was revealed to enhance resistance against TSWV thereby delaying virus accumulation and symptom expression [39, 72]. Moreover, PR-10 and *Sw-5b* were significantly upregulated in the tomato plant infected by TSWV [79]. PR protein is usually accumulated in plants upon the pathogen attack and it is particularly stimulated as a defence response via local and systemic acquired resistance which could impair viral movement [72, 79]. MADS-box genes have been implicated for possible involvement in SW-7 resistance status as they were stimulated in the SW-7 resistance line against TSWV [72]. The MADS-box genes code for the MADS-box proteins which are conserved transcription factors (TFs) with diverse biological activities such as floral development, determination of floral organ identity, floral meristem formation, and regulation of flowering time and responses to environmental cues. More so, they play an important role in regulating target genes. Additionally, they possess a weakly conserved K-box domain, facilitating the dimerization of transcription factors. These genes are categorized into various subfamilies based on their sequences, expression patterns, and functional roles and they interact with other proteins to form multi-component regulatory complexes [80, 81]. Furthermore, some upregulated genes in Sw-7 resistance line have a connection with lignin deposition, callose accumulation, transcriptional activation or repression, proteolysis and phosphorylation [72]. Similarly, a MADS-box TF was identified as one of the putative targets for TY-2 resistance in tomatoes against TYLCV [72]. However, the identification result of the TSWV resistance from natural field inoculation is difficult to reproduce owing to TSWV geographical distribution specificity [39]. Therefore, molecular linkage markers were primarily developed for *Sw-5* and *Sw-7* genes [39].

Tomato mosaic virus (ToMV) (*Tobamovirus tomatotessellati*), which belongs to the family Virgaviridae, is mainly transmitted through mechanical contact during farm operations. It is challenging to control it, because infected seeds can also transmit the virus. Its symptoms include stunted growth, mottling appearance, and reduction in fruit production. The degree of the symptoms is determined by the host genotype, age, environmental conditions, and the occurrence of recombinants among the isolates [62, 82]. Nevertheless, dominant R-genes (*Tm-1*, *Tm-2* and *Tm-2*^{2}) were incorporated into some susceptible lines to confer resistance on the tomato plants through introgression, particularly *Tm-2*^{2}, which is a broad-spectrum resistant gene and has been proven to be potent and stable over the years until recently when a novel *Tobamovirus* species known as tomato brown rugose fruit virus (ToBRFV) (*Tobamovirus fructirugosum*) emerged and infects tomato lines carrying *Tm-2*^{2} [2, 52, 62, 83–86].

The symptoms of ToBRFV depend on age, cultivar and environmental conditions with yellowing and plant wilting in case of severe infection. It is transmitted primarily through mechanical means, contaminated seeds and contact with infected plants. The presence of *Tm-2*^{2}/*Tm-2*^{2} in homozygous form does not hinder ToBRFV multiplication. ToBRFV movement protein (MP) escaped from being recognized by *Tm-2*^{2} and its MP possesses an important residual amino acid reported to be responsible for its action [82, 86, 87]. However, ToBRFV MP is not as effective as tobacco mosaic virus (TMV) (*Tobamovirus tabaci*) MP (TMV is similar to ToMV) for viral cell-to-cell transportation. Therefore, it was speculated that the emergence of ToBRFV through adaptation to *TM-2*^{2} in tomato plants might not be unconnected to fitness costs. Cultural control has not achieved much success and therefore, the search for new resistance cultivars has to be continued [82, 86, 87]. In *Arabidopsis*, a homologous *Tobamovirus* S-gene, TOBAMOVIRUS MULTIPLICATION 2 A (TOM2A) was identified and its mutated version was revealed to be recessive genes for TMV in *Niacotiana tabacum* L. TOM2a is strongly

conserved, and its loss-of-function is prevented by selective pressure. The artificial knockout (KO) of TOM2A orthology in tomato plants conferred resistance against ToMV and TMV, suggesting it is a promising genetic molecule to be explored in developing tomato resistance lines against ToBRFV [88].

Another novel virus recently discovered is tomato mottle mosaic virus (ToMMV) (*Tobamovirus maculatessellati*). Its symptoms include mottling, necrosis and leaf distortion. ToMMV replication is highly suppressed in *Tm-2*^{2}/ *Tm-2*^{2} homozygous and *Tm-2*^{2}/ *Tm-2* heterozygous plants whereas *Tm-2*^{2}/ *tm-2* heterozygous tomato plants were infected by ToMMV [50]. *Tm-2*^{2} gene confers resistance on the host plants against tobamoviruses by identifying and suppressing viral MP [87]. The momentary expression of ToMMV MP in the leaves of Tm-2^2*N. benthamiana* Domin, stimulated hypersensitivity cell death-related response thereby signifying that MP of ToMMV is a virulent factor for Tm-2^2 resistance and the resistance is controlled by allele combination as well as its concentration which is influenced by the environment [87].

A cross-protection mechanism can also be employed in tomato plants to protect them against viral pathogen attacks. This is a phenomenon in which a plant previously infected by a particular virus strain shows a delay in response or is protected against the subsequent infection by a different strain of the same virus or its close relation. Therefore, a less virulent virus strain is usually selected from the natural strains or obtained by a means of artificial treatment of the virulent strains with ultraviolent irradiation, specific temperature or incubation with nitrous acid [82]. The attenuated ToMV was previously employed in tomato plants to protect them from ToMV. Through modification, a more potent resistance against ToMV can be achieved as the breakdown of Tm-2^2-based resistance continues. Such a method was recently applied to control disease caused by *Tobamovirus* in *Physalis alkekengi* Mill [82].

Other tomato viruses include tomato torrado virus (ToTV) (*Torradovirus lycopersici*), pepino mosaic virus (PepMV) (*Potexvirus pepini*), tomato infectious chlorosis virus (TICV), tomato yellow ring spot virus (TYRSV), tomato necrotic ring virus (TNRV), groundnut bud necrosis tospovirus (GBNV), cucumber mosaic virus (CMV), potato virus X (*Potexvirus ecspotati*), PVY, *Capsicum* chlorosis virus (CaCV) (*Orthotospovirus capsiciflavi*), watermelon bud necrosis tospovirus (WBNV) (*Orthotospovirus citrullonecrosis*), *Parietaria* mottle virus (PMV), tomato leaf curl New Delhi virus (ToLCNDV), (*Begomovirus solanumdelhiense*), tomato leaf curl Bangalore virus (ToLCBaV) (*Begomovirus solanumbangalorense*), tomato leaf curl virus (TLCV), and southern tomato virus (STV) [2, 62, 89–92].

In *Cucumis melo* ssp. *agrestis* (Naudin) Pangalo, the resistant gene to ToLCNDV has been identified from some cultivated lines and wild relatives. Twelve candidate genes were identified through the expression analysis of the leaves of two melon plants with contrasting genotypes [93]. One of these genes, *CmARP4* is involved in the cytoskeleton structural function which enables viral protein transportation. This candidate was suggested to be a promising gene in plant breeding and can further be explored to develop a resistant line against ToLCNDV in tomato plants [93].

Secondary metabolites

Another sustainable plant disease management is the manipulation of innate defence mechanisms. An array of naturally occurring compounds such as cell wall components and metabolic enzymes are known to be involved in the plant defence against pathogen infection and this is known as induced resistance [94]. These are biochemical compounds that have roles in molecular and cellular signalling pathways and manipulating the concentration of their components suppresses the disease development in the host plants. For instance, the cell wall being the main target of pathogen attack, its components' concentration can be manipulated to confer resistance on the host plant against the pathogens. However, environmental influence may cause resistance breakdown [94, 95]. In wheat, the repression of tryptophan, L-tyrosine, phenylalanine and isoleucine at a low temperature conferred resistance on the wheat plant against wheat streak mosaic virus (WSMV) (*Tritimovirus tritici*) which was broken down at high temperatures [95]. This metabolite concentration-modified induce-resistance is linked to lipid metabolic, amino acid metabolic, carbohydrate, alkaloids and signalling transduction pathways. This finding revealed the possible influence of global warming as a result of climate change on host plant resistance against pathogen infection [95]. In chilli leaf curl virus (ChiLCV) infected plants, there was a higher accumulation of malondialdehyde, proline, polyphenols and sugar compared with what was recorded in uninfected plants [96]. These secondary metabolites can be manipulated for the advantage of the host plants.

Transcription factors

Many genes have been identified to be responsive to pathogen attacks and some of them encode TFs [1]. These TFs play a vital role in a plant's inherent immune system; they either stimulate or suppress gene expression in response to pathogen attacks [1]. In addition, the TFs play central roles in regulating genes' response to stress and other biological processes thereby making them promising candidates for

the development of pathogen-resistance tomato plants [1]. Also, TFs are involved in PTI and ETI at different various regulatory stages; they interact with PAMPs or effector proteins to either induce or repress PTI or ETI [4].

Some families of TFs that have been indicted for being involved in immune responses against pathogens include WRKY, NAC, (NAM, ATAF, CUC), Apetala2/ Ethylene Responsive Factor (AP2/ERF), basic leucine zipper domain (b-ZIP), basic helix-loop-helix (b-HLH), Mitogen-activated protein kinases (MAPKs), PR protein, receptor-like-kinases (RLKs). For instance, TGA protein, a b-ZIP TF was reported to be involved in defence against pathogen attack [1, 38]. The overexpression of SiNAC1 from tomato in tomato leaf curl virus (TLCV) DNA, was demonstrated to enhance TLCV replication and this upregulation involves Geminivirus replication enhancer (REn) [90]. The TFs can therefore be manipulated to confer resistance on the susceptible tomato lines. Furthermore, there was an activation of WRKY16 due to ToLCNDV infection in the tomato plant. This infection also stimulated the SA response pathway as shown by a significant induction of *PR-1a*, the most important gene in the SA signalling pathway and WRKY proteins were known to induce SA [97]. Additionally, a gene that plays a very critical role in cell expansion and vein formation, *TORNADO 1* (*SlTRN1*) was highly upregulated in infected tomato plants. It was then hypothesized that stimulation of the SA network upon the ToLCNDV infection in tomato plants induces WRKY16 and subsequently regulates *SlTRN1* gene transcription. SA is the primary hormone that spreads the first layer of defence response in plants infected by biotrophic pathogens [97].

RNA interference

RNAi is a conserved regulatory functional pathway that plays a central role in controlling genes and defence against viral attack. It facilitates sequence-specific gene silencing and it is an effective technique that has been shown to be efficient in the development of viral-resistant crops [39, 67, 70, 98, 99]. The RNAi mechanism has been reported to be effective in controlling the viruses from the family Geminiviridae, which are among the deadly plant viruses causing disease [100]. RNA silencing is a natural antiviral defence machinery involved in plants' response to viral infections [101]. In plants, the RNA-dependent RNA polymerases (RdRPs) use viral small interfering RNAs (vsiRNAs) as a template for double-stranded RNA production. The viral double-stranded RNA (vdsRNAs) from viral mRNA such as TSWV is cleaved by RNase III dicer-like protein (DCLs) into vsiRNAs usually between 21 and 22 nucleotides. A vsiRNA clings to an Argonaute (AGO) and is subsequently loaded onto an RNA-induced silencing complex (RISC). This triggers complementarity and cleavage of viral targets thereby amplifying silencing [39]. Plants can prevent viral attack via their RNAi immune pathway and therefore RNAi-mediated technology can be employed in the development of tomato-resistant lines which are immune to various viral infections [39].

Conversely, RdRP1 plays dual roles; it is involved in the SA resistance pathway and it can also impede the RdRP6-mediated antiviral RNAi mechanism in plants. NSs protein secreted by the virus prevents RISC activity by clinging to AGOs and consequently suppresses the RNAi mechanism leading to the breakdown of plant resistance [39]. TuMV is an example of RNA plant viruses that exploit autophagic components to their advantage by upsetting the RNA-silencing factor [4]. In addition, a new technique in RNAi called Spray-Induced Gene Silencing (SIGS) or exogenous application of RNA molecules has been introduced which is a powerful innovative technique that leads to the production of transgenic-free crops [102, 103]. Moreover, NBS-LRR-Lipid Transfer Protein (LTP) which serves as the basal immune response against pathogens in association with the RNA silencing technique can confer resistance on the host plant against viral diseases [104].

RNA silencing connects the plant developmental pathway with response to pathogen attack via transcriptional gene silencing (TGS) and post-transcriptional gene silencing (PTGS) of unique target genes [8, 73, 89, 101, 105, 106]. ToLCNDV AC2 (transcription activator protein) and AV2 (pre-coat protein) genes were reported to repress the silencing activity of the host plant's TGS- and PTGS-mediated defence network while AC3 (Replication enhancer protein), AC4 (pathogenesis-related protein) and AC5 (which facilitates viral infection and movement) were implicated in the suppression of TGS-mediated defence network only. These genes can be manipulated to confer resistance in tomato plants against viral diseases [73]. AV1 encodes coat protein and it has been implicated in viral nucleo-cytoplasmic shuttling and AC1 (replication-associated protein) is involved in rolling circle replication; the suppression of these genes hinders virus development and replication. Silencing TYLCV AV1, AC1 and AC3 simultaneously gave 100% resistance against TYLCV while silencing these genes separately was not effective [99, 100]. Similarly, from another research by Patil et al., AC1, AC2 and AC4 (from DNA-A component) and BC1 (from DNA-B component) genes from African cassava mosaic virus (ACMV), a geminivirus, were documented to be effectively targeted by RNAi mediated mechanism and subsequently confer double resistance on cassava plant against ACMV either in combination or individually [100]. Likewise, the RNAi mechanism was successfully demonstrated to provide cross-protection on cassava plants against cassava brown streak virus (CBSV) (*Ipomovirus*

brunusmanihotis) which is responsible for cassava brown streak disease (CBSD). It was shown that the level of cross-protection corresponded with the expression level of small interfering RNAs (siRNA) [107]. Furthermore, the effective control of cassava brown streak Uganda virus (CBSUV) through RNAi technology was attributed to PTGS [108]. In plants, PTGS is an RNA-mediated virus resistance mechanism employed to suppress the expression of pathogenic virulence gene(s) [20].

Genome editing

With challenges associated with the acceptance of crop products obtained through transgenic means by the public, a new technique called genome editing has been devised therefore reducing safety issues which is of main public concern associated with previous transgenic approaches [102, 109]. Genome-editing in plants through CRISPR/CRISPR-associated protein (CRISPR/Cas) is a technology in plant breeding, which is employed in developing non-transgenic mutants with desirable traits to ensure food security. It enables an efficient, specific and targeted modification at genomic loci [38, 110] and this technique surpasses all other genetic engineering technologies [111]. With the CRISPR technique, the development of new genetic variability or desirable traits, including disease resistance, can be achieved within a short period compared with conventional breeding through introgression and mutational breeding techniques via the targeted degradation of the viral genome, modification of R-genes and transformation of susceptible (S) genes [38–40, 98, 109, 110]. The technique has been employed in some other crops and can be replicated in tomato crops to develop resistant lines [39]. Moreover, new microRNAs (miRNAs) can be generated through the mutation of the known ones using CRISPR/Cap to target new pathogen effectors in plants [109].

MicroRNAs

The small, endogenous, non-coding RNA molecules, usually between 20 and 24 nucleotides, known as miRNAs, are very crucial in the modulation of gene expression [93, 109, 112]. These small molecules are important in various plant biological processes, namely: plant growth and development as well as response to both abiotic and biotic stress conditions. They have been implicated in the modulation of the arms race between tomato plants and viruses for playing a vital role in immune regulatory pathways [15, 109, 112]. MiRNAs target many plant NBS-LLR genes or R-genes, making them essential parts of plant disease stress-signalling pathways and the basis for their involvement in some new applications adopted in modern plant breeding [109, 113]. In addition, miRNAs target TFs and hormone receptors that are pathogen attack-responsive [109].

Many miRNAs mostly conserved, are known to be involved in the host plant defence strategies. These include miR156, miR159, miR160, miR162, miR164, miR166, miR167, miR168, miR169, miR171, miR172, miR319, miR396, miR397, miR398, miR399, miR403, miR408, miR447and miR482 [15, 73, 112]. MiR156/157 which targets squamosa promoter binding protein-like (SPL) TF is not unconnected with the regulation of plant growth and development and it has been also indicted in pathogenic changes in infected tomato plants [15]. In addition, the virus genome may be targeted by miRNAs to hinder its reproduction as well as function via RNA silencing [15]. MiR398 targets copper-zinc superoxide dismutases (CSD1/2), which mops up reactive oxygen species (ROS). There is a high accumulation of ROS in plants responding to pathogen attacks, leading to oxidative stress; the modulation of miR398 and its targets can enhance the host plant's defence against the pathogen attack [15]. Moreover, miR6022, miR6023, miR6024, miR6026, and miR6027 target R-genes indicating that miRNAs have crucial roles in modulating R-genes in stimulating the host resistance against viral diseases [73, 113]. In a ToLCNDV-resistant line lacking the *Ty* gene, the *Sw5a* gene was identified, and its expression is controlled by SlMYB33, which is then regulated by miR159 [114]. The repression of *SlSw5a* through virus-induced gene silencing (VIGS) led to severe disease symptoms and increased viral titre in resistant cultivar leaves. While in plants where SlMYB33 was knocked down, there was repression of *SlSw5a*, suggesting that *SlSw5a* acts downstream of Sly-miR159-SlMYB 33 modules leading to the activation of HR thereby conferring resistance on the tomato plant [114].

The quest for understanding the role played by certain miRNAs in plant-pathogen interaction led to the designing of artificial miRNAs (amiRNAs) which target relatively conserved loci on viruses to suppress the pathogenic ability/ virulence of most virus strains even when mutations occur, thereby conferring a broad-spectrum viral resistance on plants, and many miRNAs have been successfully employed for precise silencing of viral genome in plants. The amiRNA functions are similar to those of plants' natural miRNAs [15, 89, 109]. The amiRNA is designed through the replacement of the mature miRNA sequences within the primary transcript (pri-miRNA) with customised 21-nucleotide RNA segments which correspond to viral targets and possess favourable characteristics for AGO loading [115]. It has been demonstrated that the amiRNAs-mediated technique is a promising application that can be employed in developing host plant resistance to plant viruses as it was shown by the resistance conferred on cassava plants through its application against CBSV and CBSUV [116]. Similarly,

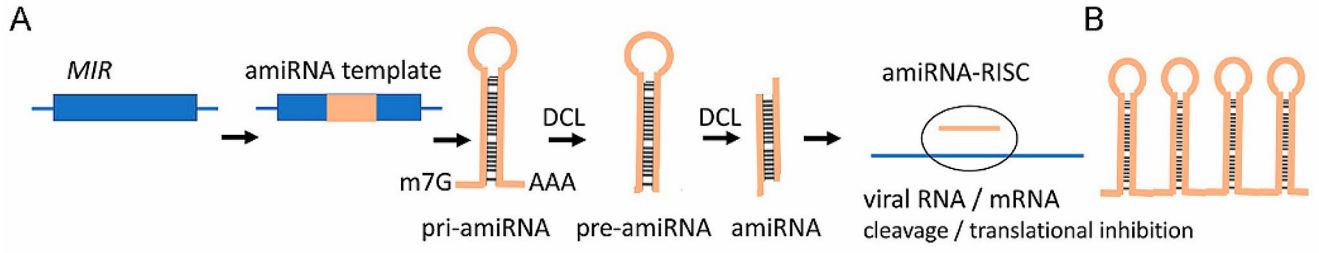

Fig. 3 The antiviral amiRNA pathway (adapted from Taliansky et al. 2021)

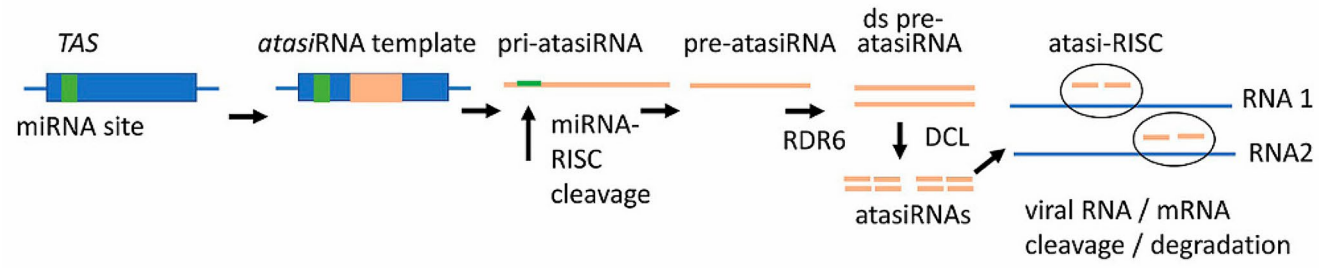

Fig. 4 The antiviral atasiRNA pathway (adapted from Taliansky et al. 2021)

an artificial miRNA (miR319a) was developed based on the sequence of miR319a from *Arabidopsis* and it was engineered to be expressed against the AC1 gene of ToLCNDV which conferred viral resistance on the commercial tomato cultivar. The ToLCNDV AC1 gene targeted by the designed amiRNA is important for its replication and virulence [89]. Moreover, the amiRNA technique has been employed to confer resistance on the tomato plant against other viruses including TSWV through RNA silencing. The amiRNA-mediated technique has an advantage over the CRISPR/Cas tool because it reduces the probability of recombination within the viral genome as well as mutant escape formation associated with CRISPR/Cas by synthesizing a short single nucleotide sequence that is complementary to the targeted viral sequence and it has become favourite in the induction of host resistance against viral attack in plants [89, 108].

However, the amiRNA-mediated approach was said to have a limitation when applied exogenously, due to the fact that the pri-miRNAs are more prone to enzymatic degradation because of their single-stranded structure (Fig. 3), when compared with double-stranded RNAs (dsRNAs) [115]. Therefore, the adoption of artificial trans-acting small interfering RNAs (atasiRNAs) will solve this problem. This is also an RNAi-mediated gene regulatory pathway. The precursors of natural tasiRNAs give perfectly paired dsRNA precursors that might be more suitable for exogenous application (SIGS application) because of their better stability as opposed to single stranded RNAs (ssRNAs) [115]. TasiRNAs are plant sequence-specific siRNAs being transcribed from TAS genes at specific loci. The tasiRNA precursor transcripts are targeted by a miRNA and thereafter, they undergo the process of maturation [117]. Some of the products from this process are converted to dsRNAs by RdRP6 (Fig. 4). Subsequently, the dsRNAs produced are cleaved into 21-nt segments (phases) by DCL4 and these are called phased siRNAs (phasiRNAs). Hence, the phased production of secondary siRNAs through next-generation sequencing is termed artificially induced phasiRNAs (atasiRNAs) [117]. The atasiRNAs have been documented to be useful in developing resistant crops against viruses. A phased siRNA developed by targeting the AC2 gene of ToLCNDV conferred resistance on tomato plants against ToLCNDV [117]. Similarly, tobacco transgenic plants that were developed through atasiRNA targeting AC2 and AC4 genes of ToLCNDV and tomato leaf curl Gujarat virus (TLCGV) showed resistance against the two viruses; the target genes are known to be RNAi suppressors [118]. The resistance level of the transgenic plants to the viruses was further demonstrated to be dependent on the quantity of siRNAs that were produced against AC2 and AC4 genes [118]. Therefore, plant viral resistance engendered through artificial phasiRNAs is a promising antiviral strategy against emerging viruses.

High-throughput sequencing

High-throughput sequencing (HTS) is a very effective technology that helps in the identification of new pathogens, tracking disease outbreaks and management of pathogens. In addition, this technology has contributed to the improvement in the understanding of the virus biology and ecology. The technique is rapid, and precise and can be employed in genetic engineering and modern plant breeding [119–121].

Moreover, resistance genes against viruses can be identified through HTS. The HTS is a next-generation sequencing innovative technique involving gene sequencing/ RNA or DNA sequencing on a large scale. The sequence of the whole viral genome from an infected plant is made possible through next-generation sequencing of total nucleic acids as well as small RNAs [122–124]. The differentially expressed genes (DEGs) in resistance and susceptible tomato lines can be characterized to elucidate their functions in pathogen defence mechanisms which will positively contribute to the emergence of pathogen resistance in tomato varieties [38]. The induction of DEGs in the resistant tomato line showed that the tomato defence response to TYLCV attack was characterized by the stimulation and regulation of a series of genes in a previous study. These genes have connections with cell wall reorganization, defence response, metabolite synthesis, transcriptional regulation and ubiquitination. Moreover, TYLCV infection could stimulate the expression of genes associated with SA biosynthesis and signalling transduction of phytohormones suggesting the importance of phytohormones in the tomato plant's defence mechanism against viruses [43, 125]. Likewise, upon the infection of tomato plants with two contrasting genotypes, R-line and S-line without known Ty resistance by ToLCBaV, many DEGs were recorded and some of them play vital roles in photosynthesis, defence response, wound response, glutathione metabolic process, toxic catabolic process, etc. [91]. Among these DEGs, there was a significant induction of MIK2-like transcripts in the R-line. The MIK2 which is situated on the plasma membrane, stimulates the basal immune response, PTI against pathogen attacks. Whereas in the S-line, Receptor-Like protein 33 was induced and it was hypothesized to serve as a negative defence response regulator [91]. Other genes that were significantly induced in the R-line include Nudix hydrolase (NUDX8), SAG 21 wound-induced basic protein and GRXC6 while EDRS was upregulated in the S-line. All these genes directly or indirectly have roles to play in defence response pathways and they should be explored in the development of broad-spectrum resistance against viral pathogen attack [91]. The challenges encountered in the deployment of HTS in modern plant breeding are primarily technical know-how and limited resources. Therefore, global collaboration and capacity building will go a long way to address these issues [125].

Mutualism

Some plant-pathogen interactions are mutualistic as revealed in the interaction between the STV and the tomato plants [92, 126]. The STV infection influences the gene expression in tomato plants, leading to the repression of ethylene-biosynthesis and signalling-related genes. The STV-infected tomato plants were reported to have superior/beneficial characteristics as opposed to uninfected plants and they can be selected artificially [127]. These double-stranded RNA viruses are derived from the virus genomes, distributed at low, stable concentrations throughout the host plant tissues, and they do not have any significant adverse effects on the host plants. Additionally, they are passed to the next generation through the seeds and this type of virus is known as persistent virus [104]. Also, mutualism was documented between beet crystic virus (BCV) and *Beta vulgaris* L. (beet plant) in which yield loss was prevented in infected beet plants under drought conditions [127].

Conclusion

Undoubtedly, the importance of the tomato plant, its genetic diversity and an array of viral diseases have emphasized its position in studying plant-pathogen interactions. The consequence of an arms race between the host plant and pathogens, determines the susceptibility of the host plants to pathogen attacks. The challenges associated with the development of new virus strains, their fast spreading and the unavailability of antiviral products have opened up new cutting-edge technologies. Due to the public concerns with respect to safety issues associated with the transgenic approaches, RNAi-mediated and CRISPR/Cap approaches have gained popularity because they can be employed to develop transgenic-free crops. In addition, they are effective, and precise and can be achieved within a short period compared with the conventional breeding technique. Therefore, these techniques can be explored to develop tomato-resistant lines against viral diseases and to achieve this, there is a need for capacity building and foreign collaborations to effectively address food insecurity globally.

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Declarations

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