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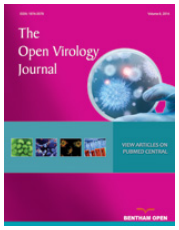

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REVIEW ARTICLE

The Evolutionary Significance of Generalist Viruses with Special Emphasis on Plant Viruses and their Hosts

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Abstract:

The host range of a virus is defined as the number of species a virus potentially infects. The specialist virus infects one or few related species while the generalist virus infects several different species, possibly in different families. Origin of generalist viruses from their specialist nature and the expansion of the host range of the generalist virus occur with the host shift event in which the virus encounters and adapts to a new host. Host shift events have resulted in the majority of the newly emerging viral diseases. This review discusses the advantages and disadvantages of generalist over specialist viruses and the unique features of plant viruses and their hosts that result in a higher incidence of generalist viruses in plants.

Keywords: Generalist viruses, Specialist viruses, Host range, Host switch, Zoonoses, Emerging diseases, Plant viruses.

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1. INTRODUCTION

Viruses can infect all the life forms from archaebacteria to eubacteria, from Protista to algae, from plants to animals [1]. They cause different diseases in plants and animals, accounting for huge economic loss in addition to the loss of lives [2, 3]. Like any other pathogens, viruses need transmission routes for their spread. Animal viruses use different transmission routes such as micro-droplets through the air, food, water, direct physical contact and vectors [4]. Since plants are sessile, most plant viruses use vectors for their transmission from one plant to another [5]. Other modes of transmission include direct entry through the site of injury caused by agricultural practices and environmental factors, vegetative propagation from infected parts, and infected seeds [6]. The most common vectors of plant viruses are insects, in addition to nematodes, arthropods, and fungi. These vectors acquire viruses from infected plants and release them when they feed on healthy plants.

A virus can infect one or more hosts and this is determined by the host range of the virus. The host range indicates the number of different hosts a virus can infect. Some viruses are highly specific and infect one or related hosts (specialist virus), while others infect more than one unrelated host (generalist virus). Generalist viruses can have a narrow host range when they infect few hosts or a wide host range when they infect a large number of hosts [7]. Examples of specialist viruses are dengue and mumps viruses, which infect only humans, while examples of generalist viruses are cucumber mosaic virus, which infects several species of plants, influenza A virus, which infects birds and several mammal species, and canine distemper virus, which infects several species of mammals [7, 8].

The host shift event is defined as an event where a pathogen encounters and adapts to a new host. The host shift is a significant event in virology. It allows the specialist virus to become a generalist by expanding its host range. The host shift event can result in the emergence of new diseases in both plants and animals and may cause huge economic loss and loss of lives. Pathogens host shifts have resulted in most of the recent emerging diseases in animals and plants [8, 10]. For example, human diseases like Avian flu, AIDS, SAARS, Dengue originated because of host shift events [8, 10]. In plants, Pepino mosaic virus, Tomato leaf curl New Delhi virus, Begomoviruses and Tospoviruses are rapidly expanding their host range, posing a serious threat to agricultural production [9 - 13].

Zoonotic diseases (zoonoses) are transmitted naturally from animals, mostly vertebrates, to humans. Zoonoses may be bacterial, viral, fungal, protozoal or any other pathogen. A study published by Taylor *et al*. [14] found that 61% of the pathogens that infect humans are zoonotic and 175 are

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associated with the emerging diseases. Among the pathogens associated with emerging diseases, 75% are zoonotic. The analysis revealed that zoonotic pathogens are twice as likely to cause emerging diseases as non-zoonotic pathogens. These pathogens are able to break the barriers of host shift events. Another study by Jones *et al*. [15] found a similar result. They also found that majority of the zoonoses linked emerging diseases (71.8%) originate in wildlife and their numbers are increasing over time. However, certain species, such as bats, serve as an exception and act as a reservoir for zoonoses [16]. Examples of some important zoonotic viral pathogens include Rabies virus, HIV, avian and swine influenza virus, SARS virus, MERS virus, Ebola virus, Nipah virus, Chikugunya virus [17 - 19], and the most recent COVID-19 virus [20, 21].

Orthoreovirus is an example zoonotic virus having a wide host range. It mainly infects mammals and some non-mammalian species of reptiles and birds [22]. They belong to reovirus and contain segmented ds RNA genome and can lead to the emergence of a pandemic strain *via* mutation and/or reassortment of the genome. Recently, members of orthoreovirus have caused zoonotic infection in humans [23, 24]. Another interesting example of a virus that causes recurrent zoonotic transmission is the influenza virus. Avian and swine influenza virus subtype A have caused sporadic infections and pandemics in the past. Aquatic birds and poultry are primary and the natural reservoirs of the Avian Influenza A virus (Bird flu). Strains that have caused the pandemics are avian influenza virus subtypes A(H5N1), A(H7N9), and A(H9N2) and swine influenza virus subtypes A(H1N1), A(H1N2) and A(H3N2). The entry of the influenza virus inside the cell is mediated by the interaction of the viral glycoprotein, hemagglutinin (HA), and the host cell surface sialic acid receptor. Since sialic acid receptors are found on the surface of human respiratory tract cells, zoonotic transmission becomes possible [25, 26].

On the other hand of the host range of viruses, lie specialist viruses. Hepatitis Delta virus (HDV) is an interesting example of it. It primarily infects humans and is one of the five hepatitis viruses. HDV has some unique features among animal viruses. It is the smallest animal virus known and contains a single-stranded circular RNA genome of just 1.7 kb. It shows similarity to viroids in genome architecture, mode of genome replication and interaction of the genome with the host proteins. HDV is a defective virus since it requires co-infection with the Hepatitis B virus for its life-cycle. Thus, HDV infection in humans occurs only in the presence of HBV infection (Superinfection) [27].

Hence, works towards understanding the host-shift events of viruses have gained momentum in recent years. This review will summarise the evolutionary advantages and disadvantages of generalist viruses over specialist viruses, adaptive challenges faced by a virus during a host shift event and the unique features of plants and their viruses that promote the generalist nature of plant viruses.

2. ADVANTAGES AND DISADVANTAGES OF GENERALIST VIRUSES

Both generalist and specialist viruses are found in nature, and it is useful to compare the evolutionary advantages and disadvantages of generalist viruses over specialist viruses, which can be summarized as follows:

2.1. Generalist Viruses have Higher Chances of Propagation

Any living organism aims to increase its population and this also applies to viruses. After completing the life cycle in a host, the virus exits and infects the same or a different host to continue the life cycle. Generalist viruses have a higher probability of finding the correct host for infection since they infect more number of species than the specialist viruses [8]. In addition, if a virus has multiple hosts, one of the hosts can act as a reservoir where, in the absence of a preferred host, the virus stays in an alternate host until the preferred host becomes available. This increases the chances of successful propagation of a generalist virus. For example, Potato leafroll virus and Potato virus Y make use of a weed, hairy nightshade (*Solanum sarrachoides*), as a viral reservoir and this increases virus infection of potato plants [28, 29]. Similarly, bats serve as a reservoir for several important human viruses like Ebola and Nipah viruses [30].

2.2. Generalist Viruses have Lower Extinction Threats

Viruses act as pathogens and hence, according to the Red Queen hypothesis, there is a race between a virus and its host, where on the one hand, the host aims to develop defense mechanisms that can either eliminate or render the virus harmless or less harmful [31 - 34], but on the other hand, the virus aims to maximize its fitness in the host [35]. Fitness is a cumulative ability of the virus to utilize the host resources for its propagation, ability to counteract the host defense network by increasing its virulence and transmission potential. Hence, with time the host may evolve to become resistant to a virus. This has been observed in plants [32]. For example, several plant species developed resistance to specific viruses through resistance genes that are either dominant or recessive in nature. Dominant resistance genes act by synthesising protein products that bind to the avirulence (Avr) proteins of the viruses, rendering the virus inactive. Recessive resistance genes code for the mutated forms of the host factors indispensable for viral propagation, as a result, the virus fails to utilise them. If both the copies of a recessive resistance gene are mutated, the virus fails to propagate in the host. Therefore, if a host develops resistance then it will pose a serious extinction threat to a specialist virus, whereas the generalist virus can complete its life cycle in its alternate host(s). In addition, if the population of one of the hosts dwindles or if the host gets extinct, a generalist virus can complete its life cycle in other hosts. However, a specialist virus may face an extinction risk with the extinction of its host. Thus, having more than one host may increase the chances of viral survival.

2.3. Generalist Nature of Viruses Aids in their Evolution

Generalist viruses propagate in more than one host. Different hosts pose varying selection pressure on the virus. This leads the virus to adapt differently in different hosts and thus, the selection of unique genotypes of the virus in each host. This can result in the evolution of a new species of the virus. The evolution aims to improve the fitness of the virus in

the given host [36]. Nonetheless, the evolved species of the virus may show fitness trade-offs in the original hosts [7, 37].

2.4. Opportunity for the Generalist Virus to Acquire New Genetic Material

The infection of a host with more than one virus has been observed [38]. Hence, a generalist virus may be exposed to different sets of genetic material in different hosts, given the host is infected with more than one type of virus at one time. However, a specialist virus will have limited exposure to foreign DNA. This provides the generalist virus higher ability to bring variations through recombination and reassortment and may lead to an evolution of a new strain/species of the virus. However, there is limited literature on this aspect of virus evolution. Reassortment was observed in the evolution of the Influenza virus since it has a segmented genome and hence viruses with different genotypes can exchange nucleic acid segments [39 - 41].

2.5. Generalist Viruses have Higher Fitness in a Dynamic Environment

In a dynamic environment, where fluctuation in biotic and abiotic factors occurs, generalist viruses have higher chances of survival. This is because generalist viruses thrive on more than one host and different hosts pose varying selection pressure on the virus. This allows the virus to adapt differently in different hosts leading to higher standing variation at any point in time. This helps the generalist virus adapts faster in a dynamic environment [42, 43].

3. DISADVANTAGES OF GENERALIST VIRUSES OVER SPECIALIST VIRUSES

3.1. Generalist Viruses Suffer from Fitness Trade-offs

Co-evolution of the virus and its host results in the specialisation of the virus, which helps the virus to improve its fitness in the host. As a result, a specialist virus can evolve to achieve maximum fitness in its host [42, 43]. However, it will be a daunting task for a generalist virus to maximise its fitness in each of its hosts [44] since higher fitness in a host may cause fitness trade-offs in other hosts and *vice-versa* [7]. Therefore, a generalist virus evolves to acquire fitness, which allows it to propagate in each of the hosts successfully, albeit with different fitness. The lower fitness of the generalist virus may be disadvantageous when it has to compete with another virus having higher fitness in a given host. The fitness cost of its adaptation in a new host could even lead to the loss of the original host(s) [7, 45].

3.2. Generalist Viruses are Disadvantageous in a Stable Environment

Over time, evolution should help the virus increase its fitness in the host until it achieves an optimum possible fitness. Since the generalist virus propagates in more than one host, it has to face different selection pressures, thus may not be able to maximise its fitness, as explained earlier. On the other hand, the specialist virus will evolve to achieve maximum fitness in its host. Hence, a stable environment favours the evolution of specialist viruses [46].

4. BARRIERS OF A HOST SHIFT EVENT BY A VIRUS

The evolution of the generalist virus from its specialist nature and expansion of the host range of the generalist virus occurs due to a host shift event where the virus encounters and adapts to a new host. However, there are certain challenges for a successful host shift event by a lytic virus (Fig. **1**) [37]. These are as follows:

(1) The landing of a virus on a new host.

(2) Virus entry inside the cell of the new host.

(3) Uncoating of the virus inside the cell to release the genomic nucleic acid.

(4) Overcoming the host defense network.

(5) The ability of the virus to utilize the host resources for multiplication.

(6) The ability of the virus to be transmitted within the host.

5. UNIQUE CASE OF PLANTS AND THEIR VIRUSES

During a host shift event, a virus has to overcome certain challenges (Fig. **1**). Yet, host shift events are common in nature and lead to the evolution of generalist viruses both in animals and plants [7, 37, 47, 48]. Research has shown that generalist viruses are common among plant viruses [47]. The following are proposed possible reasons that could explain the higher occurrence of generalist viruses in plants:

5.1. Ability of Plant Viruses to Land on a Large Number of Non-host Species

The first step for a successful host shift by a virus is to land on a new host [8]. Viruses after completing the life cycle must exit the host and land on a new host to initiate a host shift event. Different viruses exploit different transmission agents like air, food, water, physical contacts between the hosts, vectors, etc. to enhance their spread [4 - 6].

Plant viruses are transmitted mostly through vectors, the majority of which are insects, which are host generalists and feed on a wide variety of plants [7]. Other modes of transmission include the use of contaminated tools, vegetative propagation of infected plant parts, infected seed, etc [12]. These routes allow plant viruses to land on a wide variety of non-host plants (Fig. **2a**). Similarly, animal viruses can also land on a wide variety of non-hosts as they are transmitted *via* micro-droplets through the air, contaminated food and water, direct physical contact and vectors [13].

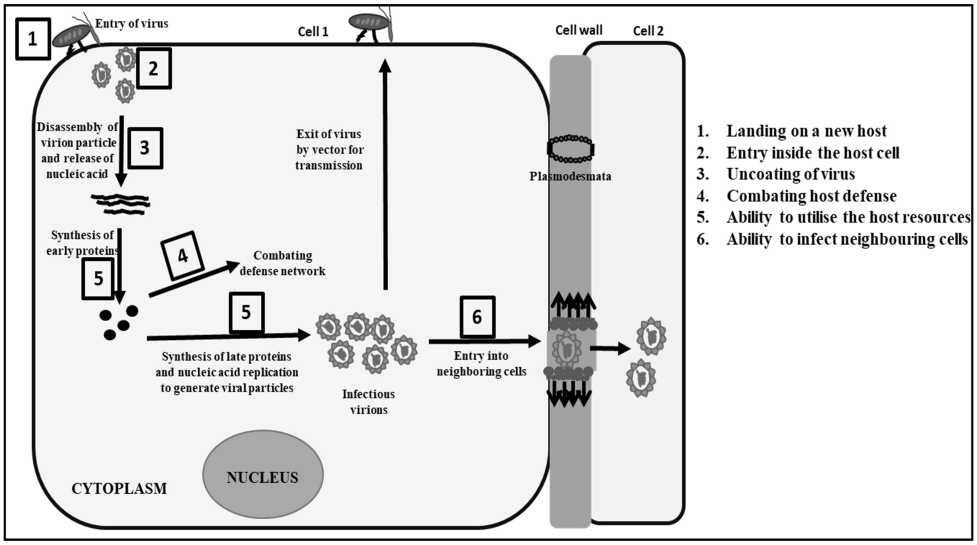

Fig. (1). Life cycle of a plant virus and challenges to a successful host shift.
Schematic representation of a plant virus life cycle. For a successful host shift, a virus has to overcome certain challenges. These challenges are indicated in black boxes (1 to 6) in the figure.

5.2. Unrestricted Entry of Plant Viruses Inside the Plant Cells

After landing on a new host, the virus or its nucleic acid must enter inside the cell for carrying out the life cycle and thus successfully achieves a host shift, and this step is one of the most challenging steps in the successful host shift event. Animal viruses enter the cell by endocytosis or membrane fusion [49], which requires specific molecular interactions between the viral surface proteins and host cell surface receptors. However, this specificity is a limitation for the entry of the animal viruses to non-host cells [8]. An analysis of 64 human viruses showed that those with the widest host range used protein receptors whose sequences were more conserved [50]. Mutation in the attachment protein of phi-6 phage allowed them to become generalists by allowing them to bind to the receptors of the non-host cells and enter the cell [51]. In the case of canine parvovirus (CPV), two mutations in the Feline panleukopenia virus surface protein allowed it to bind to canine transferrin receptor and thus expanded its host range [52, 53].

However, in the case of plant viruses, the plant cell has a rigid cell wall, and therefore, such viruses can not enter the cell similar to animal viruses. Plant viruses can only enter the cell through the mechanical injuries inflicted by either the vectors feeding on the plants, which are majorly host generalist or agricultural practices which can cause such injuries [54]. As a result, plant viruses can easily gain access to a wide variety of non-host plant species (Fig. **2b**).

5.3. Lack of a Dedicated and Robust Immune System in Plants

Host cells have developed defense mechanisms to eliminate the introduction of viruses [55]. There is a race between the virus and its host where the host aims to evolve defense mechanisms that can eliminate or render the virus harmless or less harmful. On the other hand, the virus aims to evolve to counteract the host defense mechanisms and optimise its virulence that can increase its fitness in the host [31, 34].

Once inside the cell, the virus faces the host defense network. Higher animals, such as vertebrates, have a highly developed immune system. It consists of organs and cells dedicated to mediate the defense. The immune cells scan for incoming threats and can move from one part of the body to another through motility and circulatory system. The system contains both innate and adaptive immunity. Innate immunity is broadly non-specific in nature, whereas adaptive immunity is highly specific and generates memory, which reduces the response time on successive infection by the same pathogen [56, 57].

On the contrary, the plant immune system lacks dedicated immune cells and organs. Rather, their defense network is located in each cell of the plant. Also, plants lack adaptive immunity and they only contain innate immunity, which is mainly provided by pattern recognition receptor (PRR), R-genes, RNA interference and Jasmonic acid signalling pathway [57 - 59]. RNA interference in plants is highly efficient in combating viral infections [60]. But, it employs a conserved pathway and viruses can develop resistance against the conserved proteins of the RNAi in plants [61]. Resistance in one species may be able to provide resistance in related species because of the involvement of conserved proteins.

Since plants lack adaptive immunity and dedicated immune cells and organs in vertebrates, they may not be as efficient as vertebrates in eliminating viruses during a host shift event. Thus, plants may provide a more conducive environment for a successful host shift event.

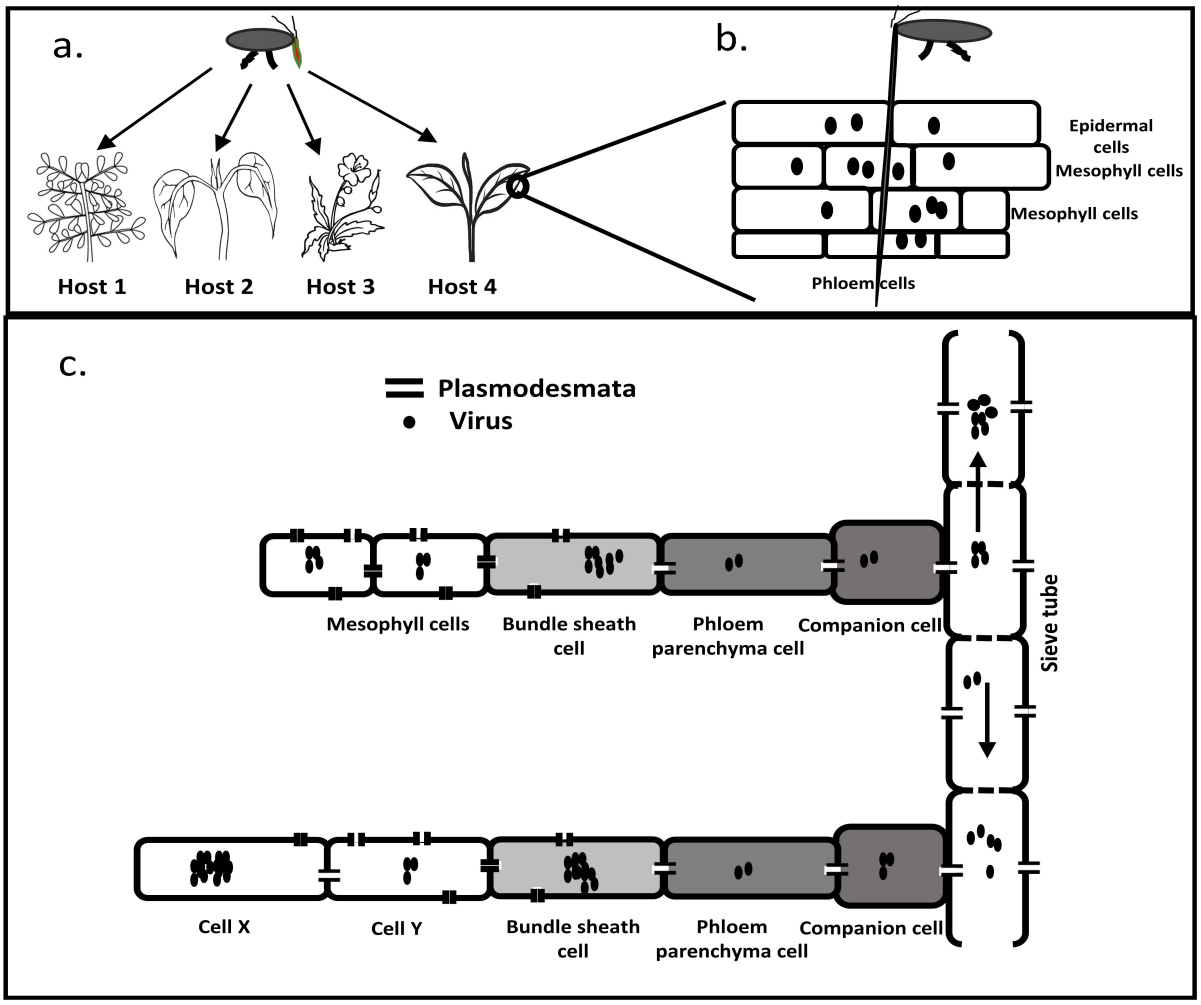

Fig. (2). Entry and spread of plant viruses**a**. Insect vectors are generalist in nature and feed on different plants. **b**. Viruses are then released through the stylet of the insect into mesophyll cells primarily. **c**. Viruses then spread to neighbouring cells and enter a sieve tube to infect distant cells *via* plasmodesmata. Viruses may experience varying fitness in different cells of the plant. For example, in the given figure, the virus experiences high fitness in bundle sheath cell and cell 'X' as indicated by the replicative potential of the virus. 'X and Y' could be any other living cells of the plant.

5.4. Majority of Plant Viruses are RNA Viruses with High Mutation Rates

Inside a non-host cell, the virus may experience lower fitness resulting in an unsuccessful host shift event. For a successful host shift event, the virus should improve its fitness in the new host. Fitness is a cumulative ability of the virus to utilize the host resources for its (i) multiplication, (ii) ability to counteract the host defense network and (iii) virulence and transmission potential. The majority of plant viruses are RNA viruses [62], and these viruses have the highest mutation rates [63]. Mutations can result in variations on which natural selection could act to improve the fitness of the virus [64]. Therefore, plant viruses can adapt faster during a host shift event. This could also explain the generalist nature of RNA viruses [37].

5.5. Plasmodesmata in Plants Provides Easy Passage of the Virus for Inter-cellular Movement

After replicating inside a cell, the virus must infect neighbouring (short distance travel) and distantly located (long distance travel) cells in a multicellular organism. However, the virus faces the cell membrane and/or cell wall as barriers while exiting the infected cell and entering a new cell. Transmission of viruses inside an organism can occur either by cell-free mode or by cell-cell connections. In cell-free mode, viruses exit the cell by exocytosis or cell lysis and diffuse to infect the neighbouring or the distantly located cells [65, 66]. In the cell-cell mode of transmission, viruses use cell-to-cell connections like a tight junction, gap junction, cytonemes, plasmodesmata, etc. for their spread. Cell-to-cell transmission is advantageous for the virus since it is faster, protects the virus from the immunological mediators like antibodies and anti-viral factors present in the extracellular space, evades the need for exocytosis or cell lysis and protects the virus from the extracellular environment, which may destabilise viruses [65 - 67].

The majority of the animal viruses use the cell-free transmission method [49, 68], whereas plant viruses exclusively use a cell-to-cell mode of transmission through plasmodesmata, which are fine cytoplasmic channels running

between two plant cells [69]. This is because plant cells have a rigid cell wall and hence viruses cannot carry out a cell-free mode of transmission. Movement through plasmodesmata is assisted by movement proteins, some of which have been found to be conserved across species (Unpublished data). Therefore, plant viruses exploit plasmodesmata to infect neighbouring cells and also enter phloem sieve elements for long distance travel to infect distantly located cells [69 - 71] (Fig. **2c**). Thus, it may be easier for a plant virus to adapt to spread inside the plant during a host shift event than animal viruses.

5.6. Plant Viruses have Access to Different Plant Cell Types and Experience Different Fitness in each Cell Type

The entry of the animal viruses inside the cell is mediated *via* a specific receptor present on the host cell surface, as explained earlier [51 - 53]. Therefore, animal viruses, after entering the organism, find the target tissue(s) and infect specific cell(s) of the tissue(s). Hence, an animal virus can only infect one or a few cell types of the organism [72]. On the contrary, plant viruses use plasmodesmata for short distance travel to infect neighbouring cells and phloem sieve elements for long distance travel to infect distantly located cells [70, 71]. Therefore, plant viruses gain access to different cell types of the plant and often lead to systemic infection [71]. Different cell types of the plant provide different cellular environments to the virus. Thus, plant viruses may experience different fitness in different cell types. This improves the chances of a virus to find the right cell type where the fitness is high and it can multiply and increase the chances of a successful host shift (Fig. **2c**).

CONCLUSION

Co-evolution of the virus and the host may result in the virus becoming more specilialised and losing its host(s) [42, 43]. However, there are certain advantages to the generalist nature of viruses, and host shift events are common in nature. The majority of the emerging viral diseases are the result of host shift events [8 - 10]. Examples of other viral diseases resulting from host shift events are SARS, MARS, Avian influenza, Ebola, HIV, etc [8 - 10]. As discussed above, host shift events in plants are easier to achieve and pose a serious threat to agricultural productivity. However, emerging plant viral diseases do not get the same attention as animal viral diseases and hence there are limited studies in this regard for plant viruses [9, 12, 13]. Understanding the mechanism of the host shift events can help us predict the potential hosts of a virus and devise strategies to manage them. Wildlife can act as reservoirs for many zoonotic viruses [73]. Due to globalisation and the encroachment of humans into the wildlife habitats, diversity of wildlife animals and the viruses and climate change, the emergence of new zoonotic diseases poses a threat to global health. Therefore, research aiming at their discovery, surveillance and understanding should be encouraged [74 - 76]. This review is intended to encourage the scientific community to further investigate and understand molecular mechanisms of host shift events of viruses, with the hope that in the near future, the scientific community will be able to predict the future hosts of viruses and be prepared to better cope with their negative effects.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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

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