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Overview of Diverse Universe of Mycoviruses and Their Role in Pathogenesis of Fungi

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Abstract

All key families of plant-infecting fungi have been observed to be infected by mycoviruses, which are substantial and ubiquitous viruses. Mycoviruses, like all other plant and animal viruses, must reproduce in live cells. These viruses spread either during spore production or cell division. Few mycoviruses are known to have a positive single-stranded RNA genome, while the majority have double-stranded RNA genomes. Few mycoviruses have been identified as the causative agents of triggering atypical pigmentation and sporadic growth to alter the sexual reproduction of the host. These viruses are categorized into taxonomic groups as developed from plant viruses. mycoviruses are notable due to their amazing capacity to cause a dramatic decrease in the virulence (hypovirulence) of the host. It has been observed that mycoviruses do not necessarily cause hypovirulence, but they also impart hypervirulence to the host fungi. The current effort summarizes the data regarding mycoviral diversity, taxonomy and their role in the pathogenesis of pathogenic fungi.



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Introduction

Mycoviruses typically infect different classes of fungi and are observed to be in association with pathogenic fungal agents, especially infecting plants. These viruses are commonly associated with all major phyla of fungi. These viruses exist in the dormant phase and infrequently cause ailment [1-3]. With notable exceptions, mycoviruses are still less thoroughly researched than viruses that attack plants and mammals. Mycovirus illnesses have little economic impact, the fungal research group is comparatively small, as well as most of the mycovirus illnesses are silent. The intensity of mycovirus investigation, though, has significantly accelerated in the last years as a result of the growing curiosity about mycoviruses. In their hosts, this phenomenon has been prompted, in particular, by a rise in studies of mycovirus-induced morphological modifications, which are thought to be both intrinsically intriguing and potentially useful [4]. Advanced technologies in molecular mycovirus have shown the usefulness of mycoviruses as instruments for examining the processes driving fungal physiology and controlling the fungal host. The ability to easily manipulate the genetic makeup of both a virus and its eukaryotic target is a unique capability thanks to developments in the genetics of filamentous fungi. In the host fungi, some mycoviruses are observed to impart noticeable modifications, such as asymmetrical development, metamorphosed sexual reproduction and anomalous coloring [5, 6]. Hypovirulence is the utmost significant feature they display the capability to decrease the virulence of infective fungi [1, 7-10]. The occurrence of mycoviruses opens up the gates in the field of investigational mycology.

History of Mycoviruses

Siden and Hauser [11] first identified a disease in the cultivated fungus *Agaricus bisporus* in 1950. This mushroom resulted in irregular fruiting bodies, early tissue deformation, and a subsequent decrease in yield [7, 12, 13]. Following this, Hollings and colleagues discovered three more anatomically unique viruses linked to ill mushrooms [14-16]. Mycoviruses were found in *A. bisporus* in substantial numbers between 1962 and 1966, according to reports. Mycovirus evidence, other than that of *A. bisporus*, was documented before 1968. As early as 1936, probable evidence for the yeast virus was presented [17]. In fungal groupings, numerous more viruses have been found. These mycoviruses were found in two different *Penicillium* species (*Penicillium*

stoloniferum and *P. funiculosum*). Mycoviruses are noticed to have traits in common including both plants and animals; however, they also exhibit some unique traits. For example, they lack motion proteins, spore formation, intracellular transmitting behavior, and extracellular ways of disease that are necessary for plant and animal viruses to accomplish their life cycles. According to some taxonomist accounts, 30% of mycoviruses have positive-sense single-stranded RNA (+ssRNA) genomes, while the majority of mycoviruses have double-stranded RNA (dsRNA) genomes [18-20]. A *Gemini* group virus associated with mycoviruses has been newly informed [7, 21, 22].

Diversity of Mycoviruses

Mycoviruses are recognized for root infection in many different phyla of fungi, including Basidiomycota, Ascomycota, Zygomycota, Chytridiomycota and Deuteromycota [23, 24].

Mycoviruses infecting Basidiomycota

Mushroom growers noticed a widespread issue in the 1950s, which they dubbed "*The illness in the harvest*". The deformed shape and drastically decreased yields of the affected mushroom were visible. A *Laccaria laccata* sporophore abnormality was identified in Czechoslovakia by Blattny and Pilate [25]. When irrigated on a healthy developing sporophore, extract from a diseased sporophore causes aberrant sporophores to proliferate in the following years. While a typical sporophore carried on growing and producing mycelium that was normally productive [26]. *Cantharellus infundibuliformis*, *C. cibarius*, and *Armillaria mellea* all showed the same abnormalities, but no viral particles were found [26, 27].

Mycoviruses infecting *Rhizoctonia* species

The significant soil-borne fungal pathogen (necrotrophic) *Rhizoctonia solani* have its place in the family basidiomycetes [28, 29]. Though, different-sized dsRNA aspects were noticed in normal progeny in AG1 to AG-13 whereas characterization of just 4 mycoviruses was done. Two dsRNA genomes having sizes of 6.4 kb and 3.6 kb, correspondingly were isolated from strain Rbs 1A1 of *R. solani* AG-3. M1 showed phylogenetical relation with *Bromoviruses* of plants and was found to be linked with improved potency and pathogenicity. While M2 was found associated with Mitoviruses and known to cause hypovirulence [30, 31]. The Rhs 717 virus was

purified from Rhs 717 strain of *R. solani*. AG-2 was identified as a *Partitivirus* [32].

***Rhizoctonia solani* infecting mycoviruses**

The primary dsRNA component in *R. solani* was originally defined by Castano and Butler [33]. Since then, several investigations have been executed to determine the varied particles of viruses that infect *R. solani*.

Mycoviruses infecting fungi imperfection

This category of fungi is much significant for their reputation in the synthesis of antibiotics. For example, antiviral features are found in filtrate attained from various species throughout the past years for instance, *P. stoloniferum* [44-46], *P. funiculosum* [47-49], *P. cyclopium* [50-52], *P. cyaneo-fulvum* [53, 54] and *Aspergillus niger* [55-57]. Lampson et al. [58] recognized virus-like particles in *P. funiculosum* in some statolon preparation [59]. The Department of Biochemistry, Imperial College London showed that *P. funiculosum* and *P. stoloniferum* were infected by a virus comprising dsRNA, which was known to initiate, in mice, the production of interferon [60].

Ascomycota infecting mycoviruses

The rest of the viruses mentioned, except for the fungus virus, are thought to be isometric. Ascomycetes *Peziza astracoderna* included lone rod-like particles [61]. Some isolated, highly purified apothecia had stiff, TMV-like 17×350 nm rods. However, their vaccination did not result in TMV indications. The virus was distinct from TMV antigenically [62]. Additionally, aberrant yeast was shown to contain virus-like particles [63]. They had a bilayer membrane and were 100 nm thick. They were unique in comparison to other fungi viruses.

Mycoviruses infecting Cryphonectria parasitica

Cryphonectria parasitica, an ascomycetes fungus, causative agent of chestnut blight [64, 65], which has been a catastrophe for *Castanea dentata* (American chestnut) in together North America as well as Europe [66, 67]. *Cryphonectria hypovirulence virus-1* CHV1 is hypovirulence-related mycovirus of the *C. parasitica* and it was initially investigated in 1991 [68-70]. Knowing the biological features of CHV1, International Committee on Taxonomy of Viruses (ICTV) recognized a new family *Hypoviridae* [71, 72]. *Hypoviridae* contains only one genus of *Hypovirus*. Family *Hypoviridae* contains four species

that were isolated from *Cryphonectria parasitica*, that belongs to the genus *Hypovirus* and are designated as *C. hypovirus* 1 [73, 74], *C. hypovirus* 2 [75], *C. hypovirus* 3 [76] and *C. hypovirus* 4 [77]. The influence of *C. parasitica* on the virulence of these species was dissimilar. Three more viruses besides these hypoviruses were identified in *C. parasitica*. Two of these viruses were *Cryphonectria parasitica mycoreovirus* 1 isolated from hypovirulent strain 9B21 and *Cryphonectria parasitica mycoreovirus* 2 isolated from hypovirulent strain C18 [78]. Third isolated virus was *Cryphonectria parasitica mitovirus* 1, belonging to the mitovirus of Nanoviridae, identified from hypovirulent strain NB631 [79].

Mycoviruses infecting Sclerotinia sclerotiorum

Ascomycetous plant pathogenic fungus *Sclerotinia sclerotiorum* infects more than 300 types of plant hosts [8]. *Sclerotinia sclerotiorum* swarms many mycoviruses, together with single-stranded circular DNA mycovirus, ssRNA viruses and dsRNA viruses [80]. The primary DNA mycovirus that was known to cause infection and confer reduced virulence to fungi was *S. sclerotiorum* hypovirulence-associated DNA virus 1 (SsHADV-1) [81]. This was plant geminivirus-associated mycovirus. *S. sclerotiorum* debilitation-associated RNA virus (SsDRV) and *S. sclerotiorum* RNA virus L (SsRV-L) have RNA (genome) that encodes for RNA replication enzyme (replicase). *S. sclerotiorum* partitivirus SsDRV is associated with *Alphaflexiviridae* in addition characterizes many associates of the genus *Sclerodarnavirus*. The SsRV-L is found to be associated with rubi-like viruses and the human pathogenic hepatitis E virus. A partitivirus (SsPV-S) along with an uncategorized non-segmented dsRNA virus, such as *S. sclerotiorum* non-segmented virus L, were identified as coinfection agent of a virulent strain.

The protein coat of SsPV-S displays a high similarity with indole-3-acetic acid (IAA) and ILR2 (leucine-resistant protein 2) of *Arabidopsis thaliana* [82]. A virus namely SsHV1 was identified, which was found to have a close association with both CHV3 as well as CHV4 in the *Hypoviridae* family [83]. Recently isolated, identified and characterized a new hypovirus namely SsHV2 was found to share a high degree of genome character with CHV1 and CHV2. At present, hypoviruses are being identified in *Valsa ceratosperma* and *Fusarium graminearum* [84]. Many *S. sclerotiorum* mycoviruses are yet to be characterized [85]. Categorized hypo virulent strain

XG36-1, that displays an infectious character. But neither DNA nor RNA extricates was obtained effectively. Two mycoviruses were isolated, and characterized, from a hypovirulent strain (strain KL-1) belonging to *S. sclerotiorum* [80]. The KL-1 was isolated from sclerotium on an infected lettuce farm in Lexington, KY, USA. This mycelial strain contained two dsRNA viral genome segments, dsRNA1 and dsRNA2, which were named *S. sclerotiorum* mitovirus-1 (SsMV1/KL-1) and *S. sclerotiorum* mitovirus-2 (SsM2/KL-1) [80]. *S. sclerotiorum* deltaflexivirus 2 (SsDFV2) is the first ever reported (+)ssRNA mycovirus that can control the incompatibility system of vegetation to diffuse between the host population [85].

Mycoviruses of *Fusarium*

Fusarium is a significantly widely distributed plant pathogenic genus [86]. Some species not only reduce yield production and value of cereals but produces toxins in crops which can disturb the health of animal and human. Now, mycoviruses have been reported in *Fusarium graminearum*, *F. solani*, *F. oxysporum*, *F. poae*, *F. virguliforme* and *F. boothii* [80, 83, 87-90]. *Fusarium* viruses belong to *Totiviridae*, *Partitiviridae* and *Chrysoviridae* [91]. However, many mycoviruses were recognized to infect the *Fusarium* species, but the *F. graminearum*-virus 1-DK2 1 (FgV1),

especially, confers hypovirulence to the host [84]. A new mycovirus recently isolated from strain HN10 of *F. graminearum* was reported [84]. This mycovirus, named (FgHV1), was almost associated with CHV1 and CHV2. It has a slight influence on the conidial synthesis and the growth rate of mycelia. It imparts no substantial influence on the virulence and production of mycotoxins.

Diversity of mycoviruses in *Fusarium*

During the past few years, the data of the miscellany of identified mycoviruses has rapidly amplified and this is because of the development and extensive use of next-generation sequencing techniques (NGS). Currently, full genome sequences are existing for twenty-nine mycoviruses from six recognized or tentatively nominated families (*Megabirnaviridae*, *Fusagraviridae*, *Partitiviridae*, *Alternaviridae*, *Crysoviridae*, *Totiviridae*) and one deallocated of group dsRNA, one deallocated (+)ssRNA virus belonging to Mymonaviridae family, and eleven (+)ssRNA viruses belonging to five recognized or temporarily nominated families (Table 1).

Viruses of *Phycomycetes*

Several phycomycetes species have been shown to transmit viruses [116]. Researchers experimented by infecting specie of *Pythium* with TMV. For this, they

Table 1: Typical viruses identified that infect *Rhizoctonia solani*.

Genome	Mycovirus	Family	Host (strain)	Reference
(+)ssRNA	barnavirus 1	<i>Barnaviridae</i>	DV-8	[34]
(+)ssRNA	beny-like virus 1 BR2	<i>Benyviridae</i>	Ag-2.2 L-P BR2	[35]
(+)ssRNA	beny-like virus 1 42304-9a	<i>Benyviridae</i>	42304-9a	[34]
(+)ssRNA	ourmia-like virus 1	<i>Botourmiaviridae</i>	RsAG2	[34, 35]
(+)ssRNA	Cucumber mosaic virus	<i>Bromoviridae</i>	Ag-3	[36]
(+)ssRNA	flexivirus 1	<i>Deltaflexiviridae</i>	DC17, AG2-2 IV	[37]
(+)ssRNA	endornavirus RS002	<i>Endornaviridae</i>	Ag-3-PT RS002	[35]
(+)ssRNA	endornavirus 2 Illinois1	<i>Endornaviridae</i>	Illinois1	[35]
(+)ssRNA	hypovirus 1	<i>Hypoviridae</i>	AG-2.2 L-P BR20	[35]
dsRNA	megabirnavirus 1	<i>Megabirnaviridae</i>	Ag2-2 IV DC17	[35]
dsRNA	virus 717	<i>Partitiviridae</i>	Ag-2 Rhs 717	[32]
dsRNA	partitivirus 2 GD-11	<i>Partitiviridae</i>	IA GD-11, Ag-1	[38]
dsRNA	dsRNA virus 2 A	<i>Partitiviridae</i>	Ag-2.2 LP A	[35]
(+)ssRNA	positive-stranded RNA virus 1	<i>Tymoviridae</i>	Illinois1	[34]
dsRNA	bipartite-like virus 1	<i>Bipartitiviridae</i>	Ag-2.2 LP BR1	[35]
(-)ssRNA	Negative stranded RNA virus 1	<i>Betamycoserpento viridae</i>	Dk13-1	[32, 34]
(-)ssRNA	Negative stranded RNA virus 2	<i>Betamycoserpento viridae</i>	248-36	[35, 39]
(+)ssRNA	fusarivirus 1 BR18	<i>Fusariviridae</i>	Ag-2.2 LP BR18	[35, 37]
(+)ssRNA	alphavirus-like 1 BR15	<i>Mycoalphaviridae</i>	Ag-2.2 LP BR15	[35]
(-)ssRNA	bunya/phlebo-like virus 1	<i>Mycophleboviridae</i>	Ag-2.2 LP BR3	[35]
dsRNA	RNA virus HN008	Unclassified	HN008	[40]
RNA	putative virus 1 BR4 (RsV1/BR4)	Unclassified	Ag-2.2 LP BR4	[41]
dsRNA	M1 dsRNA	Unclassified	Ag-3 Rhs 1A	[42, 43]
dsRNA	M2 dsRNA	Unclassified	Ag-3 Rhs 1A	[42, 43]

mixed the fungal species in the virus-containing medium. The viral agent could be recovered from fungi and medium. Later, they shake it in the virus-free medium and the virus recovered from both the medium and fungi. But it was not confirmed that either the virus replicated in fungi or it was just detained in a medium inside the mycelium structure. A different virus-like particle has been reported from the specie of *Aphelidium* [117]. A total of 55 diverse mycoviruses have been recognized in 56 fungal species in 44 fungal genera (Table 2).

Viruses of *Umbelopsis*

In comparison to other fungal families like Ascomycota and Basidiomycota, the existence of viral infections in Mucoromycota has received less attention. Mycoviruses are being discovered from the early-diverging fungus genomes increasingly and more frequently nowadays. Using next-generation genotyping, researchers have identified the genomes of 11 unique dsRNA viruses in seven distinct strains of *Umbelopsis*. The viruses were characterized as

Umbelopsis gibberispora viruses 1 and 2, *U. ramanniana* viruses 5- 9, as well as *U. dimorpha* viruses 1a, 1b, and 2. (UdV2). Two open reading frames (ORFs), putatively encoding the coat protein and the RNA-dependent RNA polymerase (RdRp), respectively, are present in all the newly discovered viruses. Eight viruses (UgV1, UdV1a, UdV1b, UrV7, UrV8b, UrV8a, UgV2, and UdV2) are recognized as fitting to the genus Totivirus based on the phylogenetic deductions from the RdRp transcripts, while UrV5, UrV6a, and UrV6b are put into a yet unconfirmed but well characterized Totiviridae-related category. The unusual +1 (or 2) ribosomal frameshift that occurs in UgV1, UgV2, UdV1b, UdV1a, UdV2, UrV8b, and UrV5 is anticipated to translate ORF2 as a fusion protein and is not typical of the majority of Totivirus genus members [141].

Viruses of *Exobasidium*

Exobasidium gracile, a member of the basidiomycetous genera *Exobasidium*, is a plant disease that can cause *C. oleifera* leaflets to swell and

Table 2: Mycoviruses infecting *Fusarium*.

Genome	Mycovirus	Host	Family*	Reference	
dsRNA	FgV2	<i>F. graminearum</i> 98-8-60 strain	Chrysoviridae	[92, 93]	
	FgV_ch9	<i>F. graminearum</i> China 9 strain	Chrysoviridae	[94]	
	FpgMBV1	<i>F. pseudograminearum</i> FC136-2A strain	Megabirnaviridae	[95]	
	FodV1	<i>F. oxysporum</i> f.sp. <i>dianthi</i> 116 strain	Chrysoviridae	[96]	
	FsV1	<i>F. solani</i> f. sp. <i>robiniae</i> SUF704 strain	Partitiviridae	[97]	
	FpV1	<i>F. poae</i> A-11 strain	Partitiviridae	[98]	
	FsPV2	<i>F. solani</i> f.sp. <i>pisi</i>	Partitiviridae	[99]	
	FgAV1	<i>F. graminearum</i> AH11 strain	Alternaviridae	[100]	
	FaW1	<i>F. asiaticum</i> F16176 strain	Totiviridae	[101]	
	FiAV1	<i>F. incarnatum</i> LY003-07 strain	Alternaviridae	[102]	
	FgAV1	<i>F. graminearum</i> AH11 strain	Alternaviridae	[103]	
	FpV-2	<i>F. poae</i> SX-63 strain	Fusagraviridae	[104]	
	FpV-3	<i>F. poae</i> SX-63 strain	Fusagraviridae	[104]	
	FgV-3	<i>F. graminearum</i> DK3 strain	Fusagraviridae	[84]	
	FgV-4	<i>F. graminearum</i> DK3 strain	Unassigned	[84]	
	FgV-5	<i>F. graminearum</i> HN1 strain	Unassigned	[105]	
	FvV1	<i>F. virguliforme</i>	Fusagraviridae	[106]	
	FvV2	<i>F. virguliforme</i>	Fusagraviridae	[106]	
	(+)ssRNA	FbLFV1	<i>F. boothii</i> Ep-BL13 strain	Unassigned	[107]
		FgMTV1	<i>F. graminearum</i> SX-64 strain	Tymoviridae	[108]
		FgV1	<i>F. graminearum</i> strain DK21	Fusariviridae	[109]
		FgMV1	<i>F. globosum</i> (MAFF No. 237511)	Narnaviridae	[100]
FbMV1		<i>F. boothii</i> strain Ep-BL13	Narnaviridae	[107]	
FcoMV1		<i>F. coeruleum</i> (MAFF No. 235976)	Narnaviridae	[100]	
FcMV1		<i>F. circinatum</i> FcCa070 strain	Narnaviridae	[110]	
FgHV1		<i>F. graminearum</i> HN10 strain	Hypoviridae	[111]	
FgHV2		<i>F. graminearum</i> JS16 strain	Hypoviridae	[112]	
FIHV1		<i>F. langsethiae</i> AH32 strain	Hypoviridae	[113]	
FgDFV1		<i>F. graminearum</i> BJ59 strain	Deltaflexiviridae	[114]	
(-)ssRNA		FgNS-RV-1	<i>F. graminearum</i> HN1 strain	Mymonaviridae	[115]

* Family names are eight recognized or tentatively assigned

become thicker [142]. Three mycoviruses co-infecting the plant disease *E. gracile* strain Z-1 were identified in a recent investigation based on genealogical and molecular analysis. *E. gracile* Zybavirus 1, *E. gracile* Totivirus 1 and *E. gracile* Totivirus 2 are the names of these viruses [143].

Taxonomy and Evolution of Mycoviruses

The same classification was developed for mycoviruses by ICTV as the other viruses are classified. Their grouping produced seven groups having linear dsRNA. These are *Chrysoviridae*, *Quadriviridae*, *Endornaviridae*, *Partitiviridae*, *Megabirnaviridae*, *Retroviridae* and *Tortiviridae*. These are also categorized into 5 families with the linear genome (ss RNA); *Hypoviridae*, *Barnaviridae*, *Alphaflexiviridae*, *Narnaviridae* and *Gammaflexiviridae*. Some uncategorized linear negative-sense single-stranded RNA and spherical DNA viruses are also found [7]. Several mycoviruses synthesize dsRNA or dsRNA-related duplicating intermediates inside their host fungus. Such mycoviruses have been distinguished when purified from dsRNA [1]. This purified dsRNA produces huge mycovirus diversity. Many fungal isolates that possess dsRNA exhibit multiple patterns of dsRNA that may denote viral genomes in segmented nature. These dsRNA correspondingly, exhibit assorted contagions of over two defective RNAs or viruses [1, 107]. While investigating evolution, researchers have made a deduction that viruses in identical taxonomical families might contaminate several host species, such as animals, plants, protozoa and fungi. The current review suggested this by an example that viruses of the family *Partitiviridae* which contain dsRNA can infect plants or fungi [144]. Other fungal infecting viruses such as FgV1, CHV1-4 and Botrytis Virus X have a phylogenetical association with other plant viruses. It was found during their genome examination that their genome structure and expression approach is analogous to potex-like viruses [145]. Other viruses show a resemblance to human pathogenic Rubi like viruses and hepatitis E virus, like the virus of *Sclerotinia sclerotiorum* [8]. Two major hypotheses have been projected for the mycoviruses' origin [1]. The first hypothesis is called the "Ancient coevolution hypothesis". According to this hypothesis, the genesis of the mycoviruses is still a secret to unveil and it just echoes enduring coevolution. While another contrasting suggestion is called the "Plant virus hypothesis", which says

mycoviruses instigated from viruses of plants, *i.e.*, a plant virus wafted from plant to fungi inside the identical plant host and it was the original mycovirus [144].

Viral Families

Totiviridae

Viruses that cause infection by infective fungi are positioned in two genera of the family *Totiviridae*, *Victorivirus* and *Totivirus*. Viruses belonging to *Victorivirus* infect filamentous fungi, whereas those of the *Totiviridae* genus infect smut fungi [145].

Chrysoviridae

The *Chrysoviridae* family includes viruses having isometric symmetry of 34-39 nm with genomes that are dsRNA. This family includes a sole genus namely *Chrysovirus* with *Penicillium chrysogenum* virus (PcV). The only ICTV-documented *Chrysovirus* that attacks a plant pathogenic fungal species is *Helminthosporium victoriae* 145S virus (Hv145V). Virions of these family members contain four monocistronic dsRNA segments. The largest segment, dsRNA-1, encodes for RNA-dependent RNA polymerase while dsRNA-2 encodes to make capsid proteins (CP). The main function of dsRNA-3 and dsRNA-4 is not clear, but it is suggested that they may be virion related and may be a factor in RNA transcription. Phylogenetic analysis shows that chrysoviruses are more related to totivirus than to partitivirus [146].

Partitiviridae

This family encompasses viral agents with isometric virions ranging 34-42 nm in thickness having a genome involving two segments of dsRNA (1.4-2.3) kbp. 3 genera of *Partitiviridae* family have been discussed. Genus *Alphachryptovirus* and *Betachryptovirus* consist of viruses that infect fungal species. Both plant and fungal partitive uses display various mutual features, such as having similarities in virions particles, symptoms, infections, and genomic organization. The phylogenetic analysis suggests the likelihood of horizontal transfer between plants and fungi [147].

Positive sense RNA viruses

Several mycoviruses having ssRNA genomes that do not express any capsid protein, and are present in dsRNA replication form in their hosts, are recognized. Such viruses analogously reproduce by

replication their genome as positive-stranded RNA viruses do. Their lineage, of genes for helicase, is within the lineage of RNA which is positive-stranded. They include members of the family *Narnaviridae*. Phylogenetic investigations of RdRp family illustrate far associations between *Narnavirus* and bacteriophages fitting to the family *Leviviridae*. Ophiostoma mitovirus infects phytopathogenic fungi and is related to hypovirulence (the ability to reduce infection-causing properties) [148].

Family Hypoviridae and Endornaviridae

The families *Endornaviridae* and *Hypoviridae* are deficient in infectious virions [149]. The linear RNA genome of *Hypoviridae* is 9-13 kbp in size. *Helicobaridium momp* endornavirus 1 and *Phytophthora endornavirus 1* are nonphyto infecting viral agents in *Endornavirus* genus (family *Endornaviridae*) of viruses infecting plants. Endornaviruses were thought to have progressed from α -like virus which had vanished its gene responsible for capsid formation [147].

Unassigned/recently classified positive-strand RNA viruses

Many positive-strand RNA viruses are unassigned at present. Diaporthe RNA virus (DRV), Botrytis virus X (BVX), *Sclerotinia sclerotiorum* debilitation (SsRV) and Botrytis virus F (BVF) are some of these. Due to phylogenetic analysis of sinuous filamentous units and protein for coat formation, BVF goes to a new family, *Flexiviridae*. *Flexiviridae* was recently divided into three families under the order Tymovirales; *Aplhaflexiviridae*, *Betaflexiviridae*, *Gammaflexiviridae* and *Deltaflexiviridae*. BVX was recently placed in the new genus *Botrexvirus* within the recently created family *Alphaflexiviridae*. The recently created genus *sclerodarnavirus* accommodates SsDRV placed in the family *Alphaflexiviridae*. DRV is an unassigned mycovirus related to the hypovirulence of its host fungi, *Diaporthe* spp. This shows homology to non-structural carmovirus particles of positive-strand RNA viruses in the *Tombusviridae* family. Sequences

Table 3 Mycoviruses infecting different fungi.

Fungi	Reported description	References
Viruses infecting Ascomycetes		
<i>Diplocarpon rosae</i>	Isometric (34-32 nm)	[118]
<i>Neurospora crassa</i>	Isometric (60 nm)	[119]
<i>Ophiobolus graminis</i>	Isometric (29 nm)	[61, 120, 121]
<i>Peziza ostracoderma</i>	Rods (17 x 350 nm)	[115]
<i>Saccharomyces carlsbergensis</i>	Phage like	[122]
Viruses infecting Phycomycetes		
<i>Aphelidium sp.</i>	Iridescent type (f)	[123]
<i>Plasmodiophora brassicae</i>	-	[14]
Viruses infecting imperfect fungi		
<i>Alternaria tenuis</i>	Isometric (30-40 nm)	[61]
<i>Aspergillus flavus</i>	Isometric (30nm)	[124]
<i>A. foetidus S (IMI-41871)</i>	Isometric (40-42 nm)	[125]
<i>A. foetidus F (IMI-41871)</i>	Isometric (30-40 nm)	[125]
<i>A. glaucus</i>	Isometric (30-40 nm)	[61]
<i>A. niger (IMI-146891)</i>	Isometric (25 nm)	[126]
<i>Helminthosporium maydis</i>	Isometric (40 nm)	[127]
<i>Mycogone perniciosa</i>	Isometric (40 nm)	[128]
<i>M. perniciosa</i>	Rods (18 x 120 nm)	[128]
<i>Penicillium brevicompactum</i>	Isometric (40 nm)	[129]
<i>P. chrysogenum (ATCC-9480)</i>	Isometric (35 nm)	[130]
<i>P. chrysogenum (ATCC-9480)</i>	Isometric (40 nm)	[131]
<i>P. chrysogenum (NRRL-1951)</i>	Isometric (35 nm)	[132]
<i>P. cyaneo-fulvum (CMI-58138)</i>	Isometric (32 nm)	[60]
<i>P. citrinum</i>	Isometric (40-50 nm)	[59]
<i>P. funiculosum</i>	Isometric (25-30 nm)	[133]
<i>P. stoloniferum (ATCC-14586)</i>	Isometric (25-30 nm)	[133, 134]
<i>P. stoloniferum F (ATCC-14586)</i>	Isometric (32-34 nm)	[135]
<i>P. stoloniferum F (ATCC-14586)</i>	Isometric (32-34 nm)	[135]
<i>Piricularia oryzae</i>	Isometric (32 nm)	[118]
<i>P. oryzae</i>	Isometric 36 nm	[120]
<i>Sclerotium cepivorum</i>	Isometric 30 nm	[119, 136, 137]

obtained from complete cDNA copies are infection-causing when injected into the sporophore. Its isolates that were transduced show phenotypical characteristics like isolates infected naturally [148].

Role of Mycoviruses in Plant Pathogenic Fungi

Depending on the *C. parasitica* paradigm, mycoviruses especially mycovirus-induced hypovirulence have primarily been researched in plant infecting basidiomycetes and ascomycetes. They are comprised of plant (crop) pathogens like white mold pathogenic *Sclerotinia sclerotiorum*, the white root decay fungus *Rosellinia necatrix*, the rice detonation fungi *Magnaporthe oryzae*, the grey mold decay fungus *Botrytis cinerea*, and *Alternaria* species, among others. Tree pathogens like the Dutch elm disorder fungi *Ophiostoma novo-ulmi* are also included (Table 3). A variety of mycoviruses, including some that produce hypovirulence and hold promise as possible biocontrol, are accommodated by *S. sclerotiorum*, which enhances our understanding and knowledge of the mycovirome. The very first mycovirus having a negative sense single-stranded RNA genome is called *Sclerotinia sclerotiorum* negative-stranded RNA virus 1 (SsNSRV-1) [10] and is grouped alongside important human infection-causing agents including mumps, measles, Ebola, and rabies within category *Mononegavirales*. Mycovirus invasion does not always result in hypovirulence, and neither does every mycovirus reduce the pathogenicity of its fungal hosts (Fig. 1).

Mycoviruses, particularly SsHADV 1 invading *S. sclerotiorum* in *Brassica napus* [150] and Pestalotiopsis theae chrysovirus 1 infecting *P. theae* [151], have lately been proven to transform a harmful fungus into a non-pathogenic endophytic fungus that shields inhabited vegetation from other infections. A partiti virus that infects the black rot disease fungus *Nectria radicola* is an early version of hypervirulence in plant pathogenic fungi [152]. Hypervirulence is a condition in which a mycovirus increases the pathogenicity of its fungal target, a condition acknowledged as hyper virulence [153]. In plant pathogenic fungi, hypervirulence would be regarded as a negative consequence of mycovirus invasion; nevertheless, this might be complemented by other advantageous compensatory features. For instance, *Leptosphaeria biglobosa* quadrivirus 1 (LbQV-1) [154] tends to enhance the radial proliferation, plant biomass, and pathogenicity of *L. biglobosa*, that also infects *B. napus* as well as, along with the highly associated *Leptosphaeria maculans*, causes the condition called as phoma stem canker mostly in UK as well as canola blackleg mostly in USA. Simultaneously to this, *B. napus*'s exposure to *L. biglobosa* contaminated with LbQV-1 causes disease resistance, which shields the crops against the more vigorous *L. maculans* [155]. The fungus causing smut, which is dimorphic basidiomycete, *Ustilago maydis* alternates between filamentous development and yeast growth [156], and possesses a lethal yeast mechanism that is comparable to *S. cerevisiae*. Crops become resilient to *U. maydis* and kindred infections as a consequence of the infectious toxin's transgenic manifestation in *planta* [157].

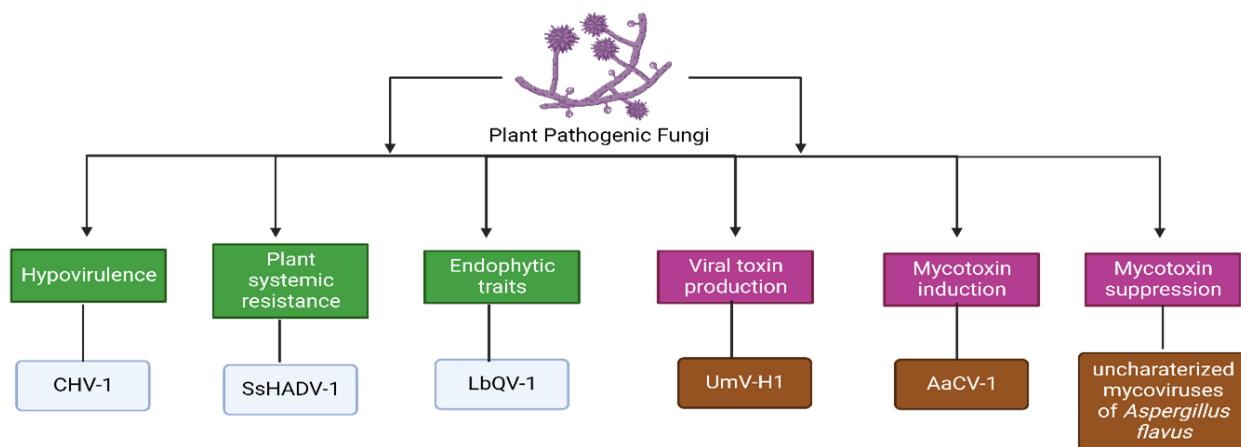


Fig. 1 Phenotypes of mycovirus in phytopathogenic fungus. Filamentous fungus that affects plants, shrubs, and agricultural crops either directly or by producing poisons have been shown to have mycovirus-induced phenotypes. With each trait, example of mycoviruses and associated host fungus are provided.

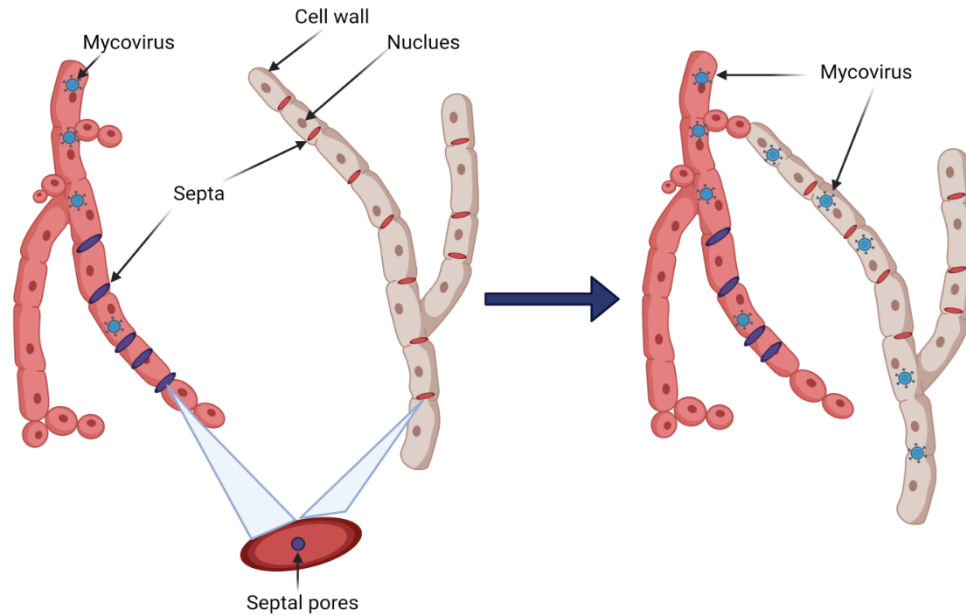


Fig. 2 Horizontal transmission of mycoviruses from infected hyphae to normal ones [160].

Quite far, it has been demonstrated that mycovirus infection alters the manufacturing of fungal toxins, suppressing the development of cancer-causing aflatoxins in *Aspergillus flavus*, the fungus that causes ear decompose, or, on the other hand, evoking the synthesis of tenuazonic acid, a supplementary chemical compound and mycotoxin, in *M. oryzae* [158] and in *Alternaria alternata*, AK-toxin [152]. Lastly, it has recently been suggested that mycovirus contamination and azole resistance are related; however, this connection has solitary been demonstrated so far in the *Penicillium digitatum*, a green mold fungus (Fig. 2) [10, 159].

Future Challenges and Conclusions

Early research on fungal infecting viruses made them objectionable since they attacked many marketable mushroom species. But after that, they were accepted as being beneficial as they can control fungal pathogenic activity. The application of mycoviruses as operative biocontrol mediators further necessitates the careful contemplation of some aspects, including both virus and host properties. Recently, *Sclerotinia sclerotiorum* hypo virulence related DNA virus 1 was utilized to control the rot disease of rapeseed stem, as an effect, this lowered the disease symptoms [8]. Mycovirolgy is currently in its early stage compared to other areas of microbiology specially discussing virology; further advancement could contribute to long-term, achieving sustainability to a number of important issues in the environment, such as

antimicrobial resistance, biological control of contagious diseases or agricultural plants, and forest management. There is a lot of unrealized promise in applied mycovirus science, as demonstrated by the most recent developments in our knowledge of linkages between mycovirus and fungus hosts. There is the possibility to employ mycoviruses more effectively and manage them to achieve their full potential if researchers have a deeper grasp of the molecular processes behind mycovirus-mediated phenotypes. In the future, there will be several challenges regarding the use of hypo virulent strains for the administration of plant infective fungi. Inhibition of mycoviruses' transmission, from hypo virulent strains to target strains due to vegetative incompatibility, will be the greater challenge. Potentially unfit hypo virulent strains may cause infections. Another important issue is the adaptation of mycoviruses to live with fungal hosts. Consequently, several mycoviruses do not disturb their host species. Some mycoviruses do not tempt infectious indications in their hosts, although they harm their host. Some mycoviruses enhance the virulence of plant pathogenic fungi by altering their phenotype.

The identification of targeted species for various fungal infections, or the acquisition of pertinent data for the treatment of these fungi-induced plant ailments, are indicated to be made possible by an awareness of mycoviral variety and approaches of new virus detection. In the upcoming years, research

on the complex interactions between viruses, fungi, plants, and environments is anticipated to rise, as well as the discovery of new mycoviruses. So, it is recommended that plenty of widely accessible data on viral sequencing besides bioinformatics tools may be employed as the first screening procedures for the construction of biological control measures in farming practices that have not yet been the research focus. It is anticipated that two approaches will be valuable to advance: in the first, the known hypovirulence implications of mycoviruses on their fungal hosts can also be implemented to related phytopathogens, aiming to reduce their growth and infectivity; in the second, hypervirulence associations can be tried in fungi known to be helpful to plants as stress-resistance stimulators, biocontrol and growth regulators. Moreover, molecular characterization or docking can be performed to find their molecular nature [161]. Virtual screening can also be performed to know these entities better [162]. Mycoviruses have a wide range of conceivable applications and substitutes as prospective biocontrol mediators in numerous fungi-plant systems, signifying a potential research field in the coming days.

Conflict of interest

The authors declare no conflict of interest.

References

- [1] Pearson MN, Beever RE, Boine B, Arthur KJMpp. Mycoviruses of filamentous fungi and their relevance to plant pathology. *Mol Plant Pathol* 2009; 10(1):115-128.
- [2] Bocos-Asenjo IT, Niño-Sánchez J, Ginésy M, Diez JJJJoMS. New insights on the integrated management of plant diseases by RNA strategies: Mycoviruses and RNA interference. *Int J Mol Sci* 2022; 23(16):9236.
- [3] Ćurković-Perica M, Ježić M, Rigling D. Mycoviruses as Antivirulence Elements of Fungal Pathogens. The Biological Role of a Virus. In: *The Biological Role of a Virus*, Springer; 2022. p. 209-249.
- [4] Filippou C. School of Life and Medical Sciences & Western Sydney University: Sydney University; 2021.
- [5] Walia A, Putatunda C, Sharma R, Sharma S, Thakur A. Biocontrol: a sustainable agricultural solution for management of plant diseases. *Microbial biotechnology in crop protection*. In: *Microbial biotechnology in crop protection*, Springer; 2021. p. 1-54.
- [6] Bist V, Srivastava S, Arkvanshi SK, Tandon A, Anand V, Kaur J, Srivastava S, et al. Microbiome Role in Control of Sustainence of Rice Health and Production. *Microbial Biotechnology in Crop Protection*. In: *Microbial Biotechnology in Crop Protection*, Springer; 2021. p. 335-393.
- [7] Ghabrial SA, Castón JR, Jiang D, Nibert ML, Suzuki NJV. 50-plus years of fungal viruses. *Virology* 2015; 479:356-368.
- [8] Jiang D, Fu Y, Guoqing L, Ghabrial SA. Viruses of the plant pathogenic fungus *Sclerotinia sclerotiorum*. *Adv Virus Res* 2013; 86:215-248.
- [9] Nuss DL. Hypovirulence: mycoviruses at the fungal-plant interface. *Nat Rev Microbiol* 2005; 3(8):632-642.
- [10] Kotta-Loizou IJ. Mycoviruses and their role in fungal pathogenesis. *Cur Opin Microbiol* 2021; 63:10-18.
- [11] Sinden J, Hauser EJMS. Report on two new mushroom diseases. *Mushr Sci* 1950; 1:96-100.
- [12] Shu L, Zeng Z, Dai J, Cheng Y, Lu Y, Chen M, et al. Morphological and metabolic changes in an aged strain of *Agaricus bisporus* As2796. *Appl Microbiol Biotechnol* 2021; 105(20):7997-8007.
- [13] O'Connor E, Doyle S, Amini A, Grogan H, Fitzpatrick DAJFB. Transmission of mushroom virus X and the impact of virus infection on the transcriptomes and proteomes of different strains of *Agaricus bisporus*. *Fungal Biol* 2021; 125(9):704-717.
- [14] Hollings MJN. Viruses associated with a die-back disease of cultivated mushroom. *Nature* 1962; 196(4858):962-965.
- [15] Hollings MJE. A virus disease of a fungus: die-back of cultivated mushroom. *Endeavour* 1963; 22:112-117.
- [16] Hollings MJMS. Some aspects of virus diseases in mushrooms. *Mushr Sci* 1965; 6:255-262.
- [17] Wiebols IG, Wieringa IK. Bacteriophagie een algemeen voorkomend verschijnsel: H. Veenman en zonen; 1936.
- [18] King AM, Lefkowitz E, Adams MJ, Carstens EB. Virus taxonomy: ninth report of the International Committee on Taxonomy of Viruses: Elsevier; 2011.
- [19] Fu M, Zhang H, Yin M, Han Z, Bai Q, Peng Y, et al. A Novel heptasegmented positive-sense single-stranded RNA virus from the phytopathogenic fungus *Colletotrichum fructicola*. *J Virol* 2022; 96(9):e00318-22.
- [20] Wang W, Wang X, Tu C, Yang M, Xiang J, Wang L, et al. Novel mycoviruses discovered from a metatranscriptomics survey of the phytopathogenic *Alternaria* fungus. *Viruses* 2022; 14(11):2552.
- [21] Zhang Y, Gao J, Li YJVG. Diversity of mycoviruses in edible fungi. *Virus Genes* 2022; 58(5):377-391.
- [22] Botella L, Jung TJV. Multiple viral infections detected in *Phytophthora condilina* by total and small RNA sequencing. *Viruses* 2021; 13(4):620.
- [23] Fahliyani AS, Rastegari AA, Yadav N, Yadav AN. Human Fungal Pathogens: Diversity, Genomics, and Preventions. In: *Recent Trends in Mycological Research. Agricultural and Medical Perspective*, Springer; 2021. p. 371-394.
- [24] Kipkemboi TP. Molecular and biological properties of diverse fungal and plant partitiviruses. PhD thesis, Okayama University, Japan; 2021.
- [25] Blatny C, Pilat A. Moznost exist-ence viros u vyssich hub. Die Moglichkeit der Existenz von Virose bei den Hutpilzen. *Ceska Mykol* 1957; 11:205-211.
- [26] Blatny C, Králík OJCM. A virus disease of *Laccaria laccata* (Scop. ex Fr.) Cooke and some other fungi. *Ceska Mykol* 1968; 22:161-166.
- [27] Linnakoski R, Sutela S, Coetzee M, Duong TA, Pavlov IN, Litovka YA, et al. Armillaria root rot fungi host single-stranded RNA viruses. *Sci Rep* 2021; 11(1):1-15.

- [28] Rafiei V, Véléz H, Dixelius C, Tzelepis GJFBR. Advances in molecular interactions on the *Rhizoctonia solani*-sugar beet pathosystem. *Fungal Biol Rev* 2023; 44:100297.
- [29] Lee D-Y, Jeon J, Kim K-T, Cheong K, Song H, Choi G, et al. Comparative genome analyses of four rice-infecting *Rhizoctonia solani* isolates reveal extensive enrichment of homogalacturonan modification genes. *BMC Genom* 2021; 22(1):1-15.
- [30] Jian J, Lakshman DK, Tavantzis SM. A virulence-associated, 6.4-kb, double-stranded RNA from *Rhizoctonia solani* is phylogenetically related to plant bromoviruses and electron transport enzymes. *Mol Plant-Microbe Interact* 1998; 11(7):601-609.
- [31] Lakshman DK, Jian J, Tavantzis SM. A double-stranded RNA element from a hypovirulent strain of *Rhizoctonia solani* occurs in DNA form and is genetically related to the pentafunctional AROM protein of the shikimate pathway. *Proceed Nat Acad Sci* 1998; 95(11):6425-6429.
- [32] Strauss EE, Lakshman DK, Tavantzis SMJM. Molecular characterization of the genome of a partitivirus from the basidiomycete *Rhizoctonia solani*. *J Gen Virol* 2000;81(2):549-555.
- [33] Li Z, Chen L, Meiling Z, Mei Y, Erxun ZJ. Diversity of dsRNA viruses infecting rice sheath blight fungus *Rhizoctonia solani* AG-1 IA. *Rice Sci* 2018; 25(1):57-60.
- [34] Marzano S-YL, Nelson BD, Ajayi-Oyetunde O, Bradley CA, Hughes TJ, et al. Identification of diverse mycoviruses through metatranscriptomics characterization of the viromes of five major fungal plant pathogens. *J Virol* 2016; 90(15):6846-6863.
- [35] Picarelli MAS, Forgia M, Rivas EB, Nerva L, Chiapello M, Turina M, et al. Extreme diversity of mycoviruses present in isolates of *Rhizoctonia solani* AG2-2 LP from *Zoysia japonica* from Brazil. *Front Cell Infect Microbiol* 2019; 9:244.
- [36] Andika IB, Wei S, Cao C, Salaipeth L, Kondo H, Sun LJ. Phytopathogenic fungus hosts a plant virus: A naturally occurring cross-kingdom viral infection. *Proceed National Acad Sci* 2017; 114(46):12267-12272.
- [37] Bartholomäus A, Wibberg D, Winkler A, Pühler A, Schlüter A, Varrelmann MJ. Identification of a novel mycovirus isolated from *Rhizoctonia solani* (AG 2-2 IV) provides further information about genome plasticity within the order Tymovirales. *Arch Virol* 2017; 162(2):555-559.
- [38] Zheng L, Zhang M, Chen Q, Zhu M, Zhou EJ. A novel mycovirus closely related to viruses in the genus Alphapartitivirus confers hypovirulence in the phytopathogenic fungus *Rhizoctonia solani*. *Virology* 2014; 456:220-226.
- [39] García ML, Dal Bó E, da Graça JV, Gago-Zachert S, Hammond J, Moreno P, et al. ICTV virus taxonomy profile: Ophioviridae. *J Gen Virol* 2017; 98(6):1161-1162.
- [40] Zhong J, Chen CY, Gao BD. Genome sequence of a novel mycovirus of *Rhizoctonia solani*, a plant pathogenic fungus. *Virus Genes* 2015; 51(1):167-170.
- [41] Zheng L, Liu H, Zhang M, Cao X, Zhou EJ. The complete genomic sequence of a novel mycovirus from *Rhizoctonia solani* AG-1 IA strain B275. *Arch Virol* 2013; 158(7):1609-1612.
- [42] Son M, Yu J, Kim KH. Five questions about mycoviruses. *PLoS Pathogens* 2015; 11(11):e1005172.
- [43] Abbas AJJoPP, Microbiology. A review paper on mycoviruses. *J Plant Pathol Microbiol* 2016; 7:12.
- [44] Powell H, Culbertson C, McGuire J, Hoehn M, Baker L. Chemotherapy. A filtrate with chemoprophylactic and chemo-therapeutic action against mm and Semliki Forest viruses in mice. *Antibio Chemother* 1952; 2(8):432-434.
- [45] Takahashi JA, Barbosa BVR, Lima MTNS, Cardoso PG, Contigli C, Pimenta LPS. Antiviral fungal metabolites and some insights into their contribution to the current COVID-19 pandemic. *Bioorg Med Chem* 2021; 46:116366.
- [46] Haq IU, Fayyaz F, Shafqat A, Basit A, Hussain F, Aziz I, et al. Natural products and SARS-CoV-2. Application of Natural Products in SARS-CoV-2. In: *Application of Natural Products in SARS-CoV-2*. Elsevier; 2023. p. 1-24.
- [47] Shope RE. An antiviral substance from *Penicillium funiculosum*. III. General properties and characteristics of helenine. *J Exp Med* 1953; 97(5):639-650.
- [48] Nißl L, Westhaeuser F, Noll M. Antimycotic effects of 11 essential oil components and their combinations on 13 food spoilage yeasts and molds. *J Fungi* 2021; 7(10):872.
- [49] Deshmukh SK, Agrawal S, Gupta MK, Patidar RK, Ranjan NJCPB. Recent advances in the discovery of antiviral metabolites from fungi. *Cur Pharma Biotechnol* 2022; 23(4):495-537.
- [50] Naficy K, Carver DH, Medicine. Cyclopin a trypsin sensitive constituent of *Penicillium cyclopium* with antiviral properties. *Proceed Soc Exp Biol Med* 1963; 114(1):175-182.
- [51] Li YH, Yang SQ, Li XM, Li X, Wang BG, Li HL. Cyclopiumolides A and B, unusual 13-membered macrolides from the deep sea-sourced fungus *Penicillium cyclopium* SD-413 with antiproliferative activities. *Bioorg Chem* 2022; 128:106104.
- [52] Petropoulos SA, Fernandes Á, Calhelha RC, Rouphael Y, Petrović J, Soković M, et al. Antimicrobial properties, cytotoxic effects, and fatty acids composition of vegetable oils from purslane, linseed, luffa, and pumpkin seeds. *Appl Sci* 2021; 11(12):5738.
- [53] Cooke PM, Stevenson JW. An antiviral substance from *Penicillium cyaneo-fulvum* biourge: I. Production and partial purification. *Can J Microbiol* 1965; 11(6):913-919.
- [54] Daudu J. Investigations on mycoviruses found in *Dothistroma septosporum* and *Beauveria bassiana* and their effects on fungal pathogenicity. 2022.
- [55] Diana S, Ana-Maria E, Lorena MA, Cristina IA, Cristina BA, Dana S, et al. Natural compounds with antimicrobial and antiviral effect and nanocarriers used for their transportation. *Front Pharmacol* 2021; 12:723233.
- [56] Androutopoulou C, Christopoulou SD, Hahalis P, Kotsalou C, Lamari FN, Vantarakis AJP. Evaluation of essential oils and extracts of rose geranium and rose petals as natural preservatives in terms of toxicity,

- antimicrobial, and antiviral activity. *Pathogens* 2021;10(4):494.
- [57] Shehabeldine AM, Hashem AH, Wassel AR, Hasanin M. *Biotechnology*. Antimicrobial and antiviral activities of durable cotton fabrics treated with nanocomposite based on zinc oxide nanoparticles, acyclovir, nanochitosan, and clove oil. *Appl Biochem biotechnol* 2022; 194(2):783-800.
- [58] Lampson G, Tytell A, Field A, Nemes M, Hilleman MR. Inducers of interferon and host resistance. I. Double-stranded RNA from extracts of *Penicillium funiculosum*. *Proceed Nat Acad Sci* 1967; 58(2):782.
- [59] Ellis L, Kleinschmidt WJN. Virus-like particles of a fraction of statolon, a mould product. *Nature* 1967; 215(5101):649-650.
- [60] Banks G, Buck K, Chain E, Himmelweit F, Marks J, Tyler J, et al. Viruses in fungi and interferon stimulation. *Nature* 1968; 218(5141):542-545.
- [61] Dieleman-Van Zaayen A. Virus-like particles in a weed mould growing on mushroom trays. *Nature* 1967; 216(5115):595-596.
- [62] Dieleman-van Zaayen A, Igesz O, Finch JJV. Intracellular appearance and some morphological features of virus-like particles in an ascomycete fungus. *Virology* 1970; 42(2):534-537.
- [63] Hirano T, Lindegren CC, Bang YN. Electron microscopy of virus-infected yeast cells. *J Bacteriol* 1962; 83(6):1363-1364.
- [64] Ahmad F, Baric SJ. Genetic diversity of *Cryphonectria parasitica* causing chestnut blight in South Tyrol (northern Italy). *Eur J Plant Pathol* 2022; 162(3):621-635.
- [65] Suzuki N, Cornejo C, Aulia A, Shahi S, Hillman BI, Rigling DJ. In-tree behavior of diverse viruses harbored in the chestnut blight fungus, *Cryphonectria parasitica*. *J Virol* 2021; 95(6):e01962-20.
- [66] Milgroom MG, Wang K, Zhou Y, Lipari SE, Kaneko SJM. Intercontinental population structure of the chestnut blight fungus, *Cryphonectria parasitica*. *Mycologia* 1996; 88(2):179-190.
- [67] Ko YH, So KK, Chun J, Kim DH. Distinct roles of two DNA methyltransferases from *Cryphonectria parasitica* in fungal virulence, responses to hypovirus infection, and viral clearance. *mBio* 2021; 12(1):e02890-20.
- [68] Shang J, Wu X, Lan X, Fan Y, Dong H, Deng Y, et al. Large-scale expressed sequence tag analysis for the chestnut blight fungus *Cryphonectria parasitica*. *Fungal Genet Biol* 2008; 45(3):319-327.
- [69] Qu Z, Fu Y, Lin Y, Zhao Z, Zhang X, Cheng J, et al. Transcriptional responses of *Sclerotinia sclerotiorum* to the infection by SsHADV-1. *J Fungi* 2021; 7(7):493.
- [70] Li K, Liu D, Pan X, Yan S, Song J, Liu D, et al. Deoxynivalenol biosynthesis in *Fusarium pseudograminearum* significantly repressed by a megabarnavirus. *Toxins* 2022; 14(7):503.
- [71] Rigling D, Hillman BI. Hypovirus. In: Tidona CA, Darai G, Büchen-Osmond C, editors. *The Springer Index of Viruses*. Springer, Berlin, Heidelberg; 2002.
- [72] Hillman BI, Milgroom MG. The ecology and evolution of fungal viruses. In: Hurst CJ, editor. *Studies in viral ecology*. John Wiley & Sons Ltd.; 2021, p. 139-182.
- [73] Hillman BI, Shapira R, Nuss DL. Hypovirulence-associated suppression of host functions in *Cryphonectria parasitica* can be partially relieved by high light intensity. *Phytopathology* 1990; 80(10):950-956.
- [74] Nuskern L, Stojanović M, Milanović-Litre M, Šibenik T, Ježić M, Poljak I, et al. Filling the gap in Southern Europe—diversity of *Cryphonectria parasitica* and Associated Mycovirus (*Cryphonectria hypovirus 1*) in Montenegro. *J Fungi* 2022; 8(6):552.
- [75] Fullbright DJP. Effect of eliminating dsRNA in hypovirulent *Endothia parasitica*. *Phytopathology* 1984; 74(6):722-724.
- [76] Linder-Basso D, Dynek JN, Hillman BIJV. Genome analysis of *Cryphonectria hypovirus 4*, the most common hypovirus species in North America. *Virology* 2005; 337(1):192-203.
- [77] Polashock JJ, Hillman BI. A small mitochondrial double-stranded (ds) RNA element associated with a hypovirulent strain of the chestnut blight fungus and ancestrally related to yeast cytoplasmic T and W dsRNAs. *Proceed Nat Acad Sci* 1994; 91(18):8680-8684.
- [78] Bolton MD, Thomma BP, Nelson BD. *Sclerotinia sclerotiorum* (Lib.) de Bary: biology and molecular traits of a cosmopolitan pathogen. *Mol Plant Pathol* 2006; 7(1):1-16.
- [79] Hillman BI, Supyani S, Kondo H, Suzuki NJ. A reovirus of the fungus *Cryphonectria parasitica* that is infectious as particles and related to the Coltivirus genus of animal pathogens. *J Virol* 2004; 78(2):892-898.
- [80] Yu JS, Lee KM, Son MI, Kim KH. Molecular characterization of *Fusarium graminearum* virus 2 isolated from *Fusarium graminearum* strain 98-8-60. *Plant Pathol J* 2011; 27(3):285-290.
- [81] Xie J, Xiao X, Fu Y, Liu H, Cheng J, Ghabrial SA, et al. A novel mycovirus closely related to hypoviruses that infects the plant pathogenic fungus *Sclerotinia sclerotiorum*. *Virology* 2011; 418(1):49-56.
- [82] Zhang L, Fu Y, Xie J, Jiang D, Li G, Yi X. A novel virus that infecting hypovirulent strain XG36-1 of plant fungal pathogen *Sclerotinia sclerotiorum*. *Virology J* 2009; 6(1):1-9.
- [83] Hamid MR, Xie J, Wu S, Maria SK, Zheng D, Assane Hamidou A, et al. A novel deltaflexivirus that infects the plant fungal pathogen, *Sclerotinia sclerotiorum*, can be transmitted among host vegetative incompatible strains. *Viruses* 2018; 10(6):295.
- [84] Marvelli RA, Hobbs HA, Li S, McCoppin NK, Domier LL, Hartman GL, et al. Identification of novel double-stranded RNA mycoviruses of *Fusarium virguliforme* and evidence of their effects on virulence. *Arch Virol* 2014; 159(2):349-352.
- [85] Chu YM, Lim WS, Yea SJ, Cho JD, Lee YW, Kim KH. Complexity of dsRNA mycovirus isolated from *Fusarium graminearum*. *Virus Genes* 2004; 28(1):135-143.
- [86] Samiksha, Kumar S. Molecular taxonomy, diversity, and potential applications of genus *Fusarium*. In: Abdel-Azeem AM, Yadav AN, Yadav N, Usmani Z, editors. *Industrially Important Fungi for Sustainable*

- Development: Biodiversity and Ecological Perspectives, Springer; 2021. pp. 277-293.
- [87] Paudel B, Pedersen C, Yen Y, Marzano SY. *Fusarium Graminearum* virus-1 strain FgV1-SD4 infection eliminates mycotoxin deoxynivalenol synthesis by *Fusarium graminearum* in FHB. *Microorganisms* 2022; 10(8):1484.
- [88] Sharma M, Singh K, Sharma SG, Kumari S, Chauhan A, Kulshrestha S. Hypovirulence-associated mycovirus in *Fusarium* sp. isolated from apple orchards of Himachal Pradesh, India. *Arch Phytopathol Plant Protec* 2021; 54(19-20):1864-1875.
- [89] Wen C, Wan X, Zhang Y, Du H, Wei C, Zhong R, et al. Molecular characterization of the first alternavirus identified in *Fusarium oxysporum*. *Viruses* 2021; 13(10):2026.
- [90] Lutz T, Japić E, Bien S, Langer GJ, Heinze C. Characterization of a novel Alternavirus infecting the fungal pathogen *Fusarium solani*. *Virus Res* 2022; 317:198817.
- [91] He Z, Huang X, Fan Y, Yang M, Zhou E. Metatranscriptomic analysis reveals rich mycoviral diversity in three major fungal pathogens of rice. *Int J Mol Sci* 2022; 23(16):9192.
- [92] Darissa O, Adam G, Schäfer W. A dsRNA mycovirus causes hypovirulence of *Fusarium graminearum* to wheat and maize. *European journal of plant pathology*, 2012;134(1):181-189.
- [93] Darissa O, Willingmann P, Schäfer W, Adam G. A novel double-stranded RNA mycovirus from *Fusarium graminearum*: nucleic acid sequence and genomic structure. *Arch Virol* 2011; 156(4):647-658.
- [94] Zhang X, Gao F, Zhang F, Xie Y, Zhou L, Yuan H, et al. The complete genomic sequence of a novel megabirnavirus from *Fusarium pseudograminearum*, the causal agent of wheat crown rot. *Arch Virol* 2018; 163(11):3173-3175.
- [95] Lemus-Minor CG, Cañizares MC, García-Pedrajas MD, Pérez-Artés E. Complete genome sequence of a novel dsRNA mycovirus isolated from the phytopathogenic fungus *Fusarium oxysporum* f. sp. *dianthi*. *Arch Virol* 2015; 160(9):2375-2379.
- [96] Nogawa M, Kageyama T, Nakatani A, Taguchi G, Shimosaka M, Okazaki M. Cloning and characterization of mycovirus double-stranded RNA from the plant pathogenic fungus, *Fusarium solani* f. sp. *robiniae*. *Biosci Biotechnol Biochem* 1996; 60(5):784-788.
- [97] Compel P, Fekete C. Genetic interrelationships and genome organization of double-stranded RNA elements of *Fusarium poae*. *Virus Genes* 1999; 18(1):49-56.
- [98] Osaki H, Sasaki A, Nomiyama K, Sekiguchi H, Tomioka K, Takehara T. Isolation and characterization of two mitoviruses and a putative alphapartitivirus from *Fusarium* spp. *Virus Genes* 2015; 50(3):466-473.
- [99] He H, Chen X, Li P, Qiu D, Guo L. Complete genome sequence of a *Fusarium graminearum* double-stranded RNA virus in a newly proposed family, Alternaviridae. *Genome Announc* 2018; 6(8):e00064-18.
- [100] Li W, Xia Y, Zhang H, Zhang X, Chen H. A Victorivirus from *Fusarium asiaticum*, the pathogen of *Fusarium* head blight in China. *Arch Virol* 2019; 164(1):313-316.
- [101] Zhang X, Xie Y, Zhang F, Sun H, Zhai Y, Zhang S, et al. Complete genome sequence of an alternavirus from the phytopathogenic fungus *Fusarium incarnatum*. *Arch Virol* 2019; 164(3):923-925.
- [102] Wang L, Zhang J, Zhang H, Qiu D, Guo L. Two novel relative double-stranded RNA mycoviruses infecting *Fusarium poae* strain SX63. *Int J Mol Sci* 2016;17(5):641.
- [103] Yu J, Kwon SJ, Lee KM, Son M, Kim KH. Complete nucleotide sequence of double-stranded RNA viruses from *Fusarium graminearum* strain DK3. *Arch Virol* 2009; 154(11):1855-1858.
- [104] Wang L, Wang S, Yang X, Zeng H, Qiu D, Guo L. The complete genome sequence of a double-stranded RNA mycovirus from *Fusarium graminearum* strain HN1. *Arch Virol* 2017; 162(7):2119-2124.
- [105] Mizutani Y, Abraham A, Uesaka K, Kondo H, Suga H, Suzuki N, et al. Novel mitoviruses and a unique tymo-like virus in hypovirulent and virulent strains of the *Fusarium* head blight fungus, *Fusarium boothii*. *Viruses* 2018; 10(11):584.
- [106] Li P, Lin Y, Zhang H, Wang S, Qiu D, Guo L. Molecular characterization of a novel mycovirus of the family Tymoviridae isolated from the plant pathogenic fungus *Fusarium graminearum*. *Virology* 2016; 489:86-94.
- [107] Kwon SJ, Lim WS, Park SH, Park MR, Kim KH. Molecular characterization of a dsRNA mycovirus, *Fusarium graminearum* virus-DK21, which is phylogenetically related to hypoviruses but has a genome organization and gene expression strategy resembling those of plant potex-like viruses. *Mol Cells* 2007; 23(3):304.
- [108] Martínez-Álvarez P, Vainio EJ, Botella L, Hantula J, Diez J. Three mitovirus strains infecting a single isolate of *Fusarium circinatum* are the first putative members of the family Narnaviridae detected in a fungus of the genus *Fusarium*. *Arch Virol* 2014; 159(8):2153-2155.
- [109] Li P, Zhang H, Chen X, Qiu D, Guo L. Molecular characterization of a novel hypovirus from the plant pathogenic fungus *Fusarium graminearum*. *Virology* 2015; 481:151-160.
- [110] Li P, Chen X, He H, Qiu D, Guo L. Complete genome sequence of a novel hypovirus from the phytopathogenic fungus *Fusarium langsethiae*. *Genome Announc* 2017; 5(9):e01722-16.
- [111] Wang S, Kondo H, Liu L, Guo L, Qiu D. A novel virus in the family Hypoviridae from the plant pathogenic fungus *Fusarium graminearum*. *Virus Res* 2013; 174(1-2):69-77.
- [112] Chen X, He H, Yang X, Zeng H, Qiu D, Guo L. The complete genome sequence of a novel *Fusarium graminearum* RNA virus in a new proposed family within the order Tymovirales. *Arch Virol* 2016; 161(10):2899-2903.
- [113] Wang L, He H, Wang S, Chen X, Qiu D, Kondo H, et al. Evidence for a novel negative-stranded RNA mycovirus isolated from the plant pathogenic fungus *Fusarium graminearum*. *Virology* 2018; 518:232-240.
- [114] Brants DHJ. Tobacco mosaic virus in *Pythium* spec. *Netherlands J Plant Pathol* 1969; 75(5):296-299.
- [115] Schnepf E, Soeder C, Hegewald E. Polyhedral viruslike particles lysing the aquatic phycomycete *Aphelidium*

- sp., a parasite of the green alga *Scenedesmus armatus*. *Virology* 1970; 42(2):482-487.
- [116] Kasvala D, Monpara P, Patel P, Upadhyay U. A review on mucormycosis. *World J Pharm Res* 2021; 10(13):1091-1112.
- [117] Tuveson R, Peterson J. Virus-like particles in certain slow-growing strains of *Neurospora crassa*. *Virology* 1972; 47(2):527-531.
- [118] Albouy J, Lapiere H. Quelques aspects de l'infection virale chez les champignons (*Sclerotium cepivorum*, *Ophiobolus graminis*, *Agaricus bisporus*). *Ann Univ A R E R S Reims* 1971; 9:333-339.
- [119] Lapiere H, Faivre-Amiot A. Presence de particules virales chez différentes souches de *Sclerotium cepivorum*. In: *Proc 8th Cong Int Prot Plant, Paris*; 1970. p 542.
- [120] Lapiere H, Albouy J, Faivre-Amiot A, Molin G. Mise en évidence de particules virales dans divers champignons du genre *Sclerotium*. *CR Acad Sci Paris Ser D* 1971; 272:2848-2851.
- [121] Volkoff O, Walters T. Virus-like particles in abnormal cells of *Saccharomyces carlsbergensis*. *J Gene Cytol* 1970; 12(3):621-626.
- [122] Aist JR, Williams P. The cytology and kinetics of cabbage root hair penetration by *Plasmiodiophora brassicae*. *Can J Bot* 1971; 49(11):2023-2034.
- [123] Mackenzie D, Adler J, editors. Virus-like particles in toxigenic *Aspergilli*. *Ann Meet Am Soc Microbiol, American Society for Microbiology, Washington, DC*; 1972.
- [124] Dieleman-van Zaayen A, Temmink JJNJoPP. A virus disease of cultivated mushrooms in the Netherlands. *Netherlands J Plant Pathol* 1968;74(2):48-51.
- [125] Ratti G, Buck K. Virus particles in *Aspergillus foetidus*: a multicomponent system. *J Gen Virol* 1972; 14(2):165-175.
- [126] Hollings M, Stone OM. Viruses that infect fungi. *Ann Rev Phytopathol* 1971;9(1):93-118.
- [127] Banks G, Buck K, Chain E, Darbyshire JE, Himmelweit F, Ratti G, et al. Antiviral activity of double stranded RNA from a virus isolated from *Aspergillus foetidus*. *Nature* 1970; 227(5257):505-507.
- [128] Bozarth RF, Wood HA, Nelson RR. Viruslike particles in virulent strains of *helminthosporium-maydis*. *Phytopathology* 1972; 62(7):748-748.
- [129] Lapiere H, Faivre-Amiot A, Kusiak C, Molin G. Particules de type viral associées au *Mycogone perniciosus magnus*, agent d'une des moles du champignon de couche. *CR Acad Sci Ser D* 1972; 274:1867.
- [130] Wood H, Bozarth R, Mislivec P. Viruslike particles associated with an isolate of *Penicillium brevicompactum*. *Virology* 1971; 44(3):592-598.
- [131] Banks G, Buck K, Chain E, Darbyshire JE, Himmelweit F. Virus-like particles in penicillin producing strains of *Penicillium chrysogenum*. *Nature* 1969; 222(5188):89-90.
- [132] Wood H, Bozarth R. Properties of viruslike particles of *Penicillium chrysogenum*: one double-stranded RNA molecule per particle. *Virology* 1972; 47(3):604-609.
- [133] Nash C, Douthart R, Ellis L, Frank RV, Burnett J, Lemke P. On the mycophage of *Penicillium chrysogenum*. *Can J Microbiol* 1973; 19(1):97-103.
- [134] Banks G, Buck K, Chain E, Darbyshire JE, Himmelweit F. *Penicillium cyaneo-fulvum* virus and interferon stimulation. *Nature* 1969; 223:155-8.
- [135] Borré E, Morgantini L, Ortali V, Tonolo A. Production of lytic plaques of viral origin in *Penicillium*. *Nature* 1971; 229(5286):568-569.
- [136] Bozarth R, Wood H, Mandelbrot A. The *Penicillium stoloniferum* virus complex: two similar double-stranded RNA virus-like particles in a single cell. *Virology* 1971; 45(2):516-523.
- [137] Ferault A, Spire D, Rapilly F, Bertrand J, Skajennikoff M, Bernaux P. Observation de particules virales dans des souches de *Piricularia oryzae* Briosi et Cav. *Ann Phytopathol* 1971; 3:267.
- [138] Yamashita S, Doi Y, Yora K. A polyhedral virus found in rice blast fungus, *Pyricularia oryzae* Cavara. *Jap J Phytopathol* 1971; 37(5):356-359.
- [139] Herrero N, Dueñas E, Quesada-Moraga E, Zabalgogezcoa I. Prevalence and diversity of viruses in the entomopathogenic fungus *Beauveria bassiana*. *Appl Environ Microbiol* 2012; 78(24):8523-8530.
- [140] Nibert ML, Ghabrial SA, Maiss E, Lesker T, Vainio EJ, Jiang D, et al. Taxonomic reorganization of family Partitiviridae and other recent progress in partitivirus research. *Virus Res* 2014; 188:128-141.
- [141] Kartali T, Zsindely N, Nyilasi I, Németh O, Sávai GN, Kocsubé S, et al. Molecular characterization of novel mycoviruses in seven *Umbelopsis* strains. *Viruses* 2022; 14(11):2343.
- [142] Teng L, Li X, Cai X, Yang S, Liu H, Zhang T. The complete genome sequence of a novel mycovirus in the plant-pathogenic fungus *Exobasidium gracile*. *Arch Virol* 2022; 167(5):1343-1347.
- [143] Zhang T, Cai X, Teng L, Li X, Zhong N, Liu H. Molecular characterization of three novel mycoviruses in the plant pathogenic fungus *Exobasidium*. *Virus Res* 2022; 307:198608.
- [144] Ghabrial SA, Nibert ML. Victorivirus, a new genus of fungal viruses in the family *Totiviridae*. *Arch Virol* 2009; 154(2):373-379.
- [145] Ghabrial S. Partitiviruses: general features. *Encyclop Virol* 2008; 4:68-75.
- [146] Hong Y, Dover SL, Cole TE, Brasier CM, Buck KW. Multiple mitochondrial viruses in an isolate of the dutch elm disease fungus *Ophiostoma Novo-Ulmi*. *Virology* 1999; 258(1):118-127.
- [147] Moleleki N, van Heerden SW, Wingfield MJ, Wingfield BD, Preisig O. Transfection of *Diaporthe perijuncta* with *Diaporthe* RNA virus. *Appl Environ Microbiol* 2003; 69(7):3952-3956.
- [148] Preisig O, Moleleki N, Smit W, Wingfield B, Wingfield M. A novel RNA mycovirus in a hypovirulent isolate of the plant pathogen *Diaporthe ambigua*. *J Gen Virol* 2000; 81(12):3107-3114.
- [149] Zhu JZ, Zhu HJ, Gao BD, Zhou Q, Zhong J. Diverse, novel mycoviruses from the virome of a hypovirulent *Sclerotium rolfsii* strain. *Front plant Sci* 2018; 9:1738.

- [150] Zhang H, Xie J, Fu Y, Cheng J, Qu Z, Zhao Z, et al. A 2-kb mycovirus converts a pathogenic fungus into a beneficial endophyte for Brassica protection and yield enhancement. *Mol Plant* 2020;13(10):1420-1433.
- [151] Zhou L, Li X, Kotta-Loizou I, Dong K, Li S, Ni D, et al. A mycovirus modulates the endophytic and pathogenic traits of a plant associated fungus. *ISME J* 2021; 15(7):1893-1906.
- [152] Okada R, Ichinose S, Takeshita K, Urayama SI, Fukuhara T, Komatsu K, et al. Molecular characterization of a novel mycovirus in *Alternaria alternata* manifesting two-sided effects: Down-regulation of host growth and up-regulation of host plant pathogenicity. *Virology* 2018; 519:23-32.
- [153] Ahn IP, Lee YH. A viral double-stranded RNA up regulates the fungal virulence of *Nectria radicola*. *Mol Plant-Microbe Interact* 2001; 14(4):496-507.
- [154] Shah UA, Kotta-Loizou I, Fitt BD, Coutts RHA. Identification, molecular characterization, and biology of a novel quadrivirus infecting the phytopathogenic fungus *Leptosphaeria biglobosa*. *Viruses* 2019; 11(1):9.
- [155] Shah UA, Kotta-Loizou I, Fitt BD, Coutts RHA. Mycovirus-induced hypervirulence of *Leptosphaeria biglobosa* enhances systemic acquired resistance to *Leptosphaeria maculans* in *Brassica napus*. *Mol Plant-Microbe Interact* 2020; 33(1):98-107.
- [156] Lai Y, Wang L, Zheng W, Wang SJ. Regulatory roles of histone modifications in filamentous fungal pathogens. *J Fungi* 2022; 8(6):565.
- [157] Clausen M, Kräuter R, Schachermayr G, Potrykus I, Sautter CJNB. Antifungal activity of a virally encoded gene in transgenic wheat. *Nat Biotechnol* 2000; 18(4):446-449.
- [158] Ninomiya A, Urayama SI, Suo R, Itoi S, Fuji SI, Moriyama H, et al. Mycovirus-induced tenuazonic acid production in a rice blast fungus *Magnaporthe oryzae*. *Front Microbiol* 2020; 11:1641.
- [159] Niu Y, Yuan Y, Mao J, Yang Z, Cao Q, Zhang T, et al. Characterization of two novel mycoviruses from *Penicillium digitatum* and the related fungicide resistance analysis. *Sci Rep* 2018; 8(1):1-12.
- [160] Kashif MJ. Mycoviruses infecting the forest pathogen *Heterobasidion annosum*: Mutual interactions and host reactions. *Dissertationes Forestales*; 2019.
- [161] Tahir RA, Wu H, Javed N, Khalique A, Khan SAF, Mir A, et al. Pharmacoinformatics and molecular docking reveal potential drug candidates against Schizophrenia to target TAAR6. *J Cell Physiol* 2019; 234(8):13263-13276.
- [162] Tahir RA, Hassan F, Kareem A, Iftikhar U, Sehgal SA. Ligand-based pharmacophore modeling and virtual screening to discover novel CYP1A1 inhibitors. *Curr Topics Med Chem* 2019; 19(30):2782-2794.