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EXPOSING HYPOVIRULENT MYCOVIRUSES FOR FUTURE MANAGEMENT OF PHYTOPATHOGENIC FUNGI

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ABSTRACT

As a result of potential application of mycoviruses for the biological control of crop fungal diseases, attention of researchers now focused on identification and characterization of viruses infecting phytopathogenic fungi. Eventhough must of mycoviruses do not have specific effects on the plants or on their hosts fungi, those that reduce the virulence of their phytopathogenic fungal hosts are highly needed to develop an alternative approach to biological control of phytopathogenic fungi, other than fungicides. Mycoviruses that infect endophytic fungi and those that encode killer toxins are also of special interest**.** Most of the previous studies mainly reported the presence of viruses in the pathogenic fungi with little information about the hypovirulence and relationships with the host plant. Hence, knowledge and understanding hypovirulence of fungal viruses is still in its infancy. Greater understanding of the viruses of fungal endophytes may therefore be helpful for practicing sustainable agriculture, particularly considering their potential application for the biological control of crop fungal diseases. Here in, we explored reports on hypovirulence of mycoviruses for future biological control against fungal diseases.

Keywords: Endophytic fungi, hypovirulence, host-plant, mycovirus

INTRODUCTION

Mycoviruses refers to viruses that infect and replicate in fungi (Ghabrial and Suzuki, 2009). Knowledge of mycoviruses is becoming wider every day since the first definitive report of viruses infecting the cultivated button mushroom *Agaricus bisporus* (Hollings, 1962). *A. bisporus*, a basidiomycete, which causes a dieback disease was the first economically important disease identified in 1948 in a mushroom house owned by the La France brothers of Pennsylvania (Sinden and Hauser, 1950). The disease hence was called La France disease, and similar diseases were reported soon afterward from Europe, Japan, and Australia. In 1962, Hollings observed and isolated at least three types of virus particles from the sporophores of diseased mushrooms and demonstrated disease transmission to symptomless mushrooms by the isolated particles, this marked the beginning of studying mycovirology. Mycoviruses are widespread in all major taxa of fungi. Their natural host ranges are limited to individuals within the same or closely related vegetative compatibility groups (Ghabrial and Suzuki, 2009) although recent advances have established expanded experimental host ranges for some mycoviruses. However, mycoviruses have attracted much attention recently for several reasons, including their coevolution with fungal hosts (Ghabrial 1998; Pearson *et al*., 2009). Moreover, many efforts have been made to identify and characterize viruses infecting phytopathogenic fungi (Xie and Jiang, 2014 ; Ghabrial and Suzuki, 2009) and the results showed that mycoviruses confered hypovirulent effect on their host fungi (Boland, 2004; Xueqiong *et al.*, 2014**;** Lifeng *et al*., 2016) hence they have the potentiality to be used in biological control of phytopathogenic fungi (Xie and Jiang, 2014). Recently, biological control has been demonstrated on many plant pathogenic fungi through applications of hypovirulent isolates to diseased plant tissues in controlled and field environments and yielded positive results. Hence, mycoviruses in particular could conceivably be exploited for biological control of their natural fungal hosts that are pathogenic for plants. Eventhough, use of chemical fungicides is one of the most reliable means of managing fungal pathogens, but their negative impact on the environment and human health has led to regulatory restrictions of its usage. Use of hypovirulent mycovirus could serve as an alternative control strategies and is environmentally safe (reduce contamination of the environment). However, despite several reports on presence of mycoviruses in fungal cells, surprisingly, to date there is scanty literature on the adoption of hypovirulence mycoviruses to manage plant pathogenic fungi, how it would be extracted and used, moreover leaving valuable sources for commercial products undiscovered. This is surprising particularly in light of the fact that recently, there were many reports of hypovirulence of mycoviruses which could be used as alternative strategies for the management of plant pathogenic fungi. In this review, we summarized the reported work on hypovirulence of mycoviruses so that more researches could be carried out to determine their efficacy on various crops, how to get (isolate) them in enough quantity, how they should be processed in to commercial products and how they should be used (applied) as biological control agents against fungal diseases.

Classification and characteristics of mycoviruses

The mycoviruses with RNA genomes are now classified into 11 families, among them, five families (Chysoviridae, Partitiviridae, Reoviridae,Totiviridae and Megabirna-viridae) accommodate undivided (family Totiviridae) or divided (4 segments for family Chysoviridae, 2 segments for families Partitiviridae and Megabirnaviridae, and 11 or 12 segments for family Reoviridae) double-stranded RNA (dsRNA) genomes which are encapsidated within capsid proteins with the formation of rigid virus particles, and the remaining six families (Alphaflexiviridae, Barnaviridae, Endornaviridae, Gammaflexi-viridae, Hypoviridae and Narnaviridae) accommodate single-stranded RNA (ssRNA) genomes, of which only two families (Alphaflexiviridae and Gammaflexiviridae) form filamentous paticles, and the other four families do not form typical virus particles (Ghabrial and Suzuki, 2009; Liu *et al.,* 2012).

Double-stranded RNA (dsRNA) viruses have been described in many fungal species, although recently single stranded RNA (ssRNA) and circular DNA (ssDNA) genomes have also been discovered (Yu *et al.,* 2010; Liu *et al.,* 2014). However, (Wang *et al.,* 2017) reported that many previously characterized dsRNA mycoviruses are supposed to be ssRNA mycoviruses at present. Also, the authors reported that according to the 9th report of the International Committee for Taxonomy of Viruses (ICTV) on virus taxonomy lists, mycoviruses are currently classified into seven dsRNA families, six ssRNA families and circular ssDNA unclassified. In most cases, there infections are latent and do not influence the host phenotype (Buck, 1998). However, in some cases these particles are useful to the host, such as the killer system in *Saccharomyces cerevisae* (Wickner,1992) and *Ustilago maydis* (Shelbourn *et al.,* 1988). Hypovirulence may also be associated with the presence of dsRNA as occurs in phytopathogenic fungi. Not all viruses are evil, and some viruses may even enhance the value, beauty, or health of their hosts (Kernbauer *et al.,* 2014; Lesnaw and Ghabrial, 2000). It is important to note, however, that despite their relatively recent discovery, fungal viruses are believed to be of ancient origins while some researchers believed that mycoviruses originate from plant viruses based on the sequence comparisons between mycoviruses and plant viruses.Thus, although lacking an extra-cellular phase to their life cycles, they nevertheless have efficient means for both horizontal and vertical transmission and are clearly very successful, being prevalent in all major taxa of fungi. Estimates of mycovirus incidence suggest that 30–80% of fungal species may be infected (Ghabrial and Suzuki, 2009).

Host Range and Transmission of Mycoviruses

Mycoviruses are not known to have natural vectors (e.g., arthropods or annelids), are commonly transmitted horizontally in nature (from a fungal strain to other fungal strains through hyphal contact or anastomosis), and are transmitted vertically in nature (transmission of mycoviruses from hyphae to the next generation through either sexual or asexual spores**).** Experimental host ranges for fungal viruses are essentially nonexistent because of lack of suitable infectivity assays. However, recent improvement of infectivity/transfection assays using purified virions or transcripts of cloned cDNAs to viral genomic RNA allowed the extension of experimental host ranges of some mycoviruses to different vegetative compatibility groups and even to different genera (Chen *et al.,* 1996; 1999). Also, recent report of amitovirus from a hypovirulent strain of the plant pathogenic fungus *Botrytis cinerea* that is phylogenetically closely related to *Ophiostoma mitovirus* 3b (Wu *et al.,* 2007), the finding raised exciting questions regarding horizontal transmission of mycoviruses between taxonomically distinct fungi. Because the mitovirus from *S. homoeocarpa* shares 92.4% nucleotide and 95.1% amino acid sequence identities with the *Ophiostoma mitovirus* 3a, the authors explained their results based on horizontal transmission and ruled out an ancient origin of the progenitor mitovirus prior to the divergence of these two distinct species of fungi. However, the authors reasoned that an extended period of coevolution with their respective fungal hosts would have resulted in a significant sequence divergence of their genomes (Ghabrial and Suzuki, 2009).

Symptoms of Mycoviruses

Fungal viruses are mainly associated with symptomless infections of their hosts. However, many studies reported that mycovirus do not always elicit obvious symptoms in their hosts and are described as causing cryptic (asymptomatic) or latent infections (Roossinck, 2008). This suggests that these viruses may be adapted to living with their hosts for long periods and that the association may even benefit both mycovirus and fungus (Roossinck, 2011). Some of the macroscopic symptoms caused by fungal viruses, includes; reductions in pigmentation and sporulation, reduction in growth, excessive sectoring and aerial mycelial collapse. These happened as a result of alterations in complex physiological and biochemical processes involving interactions between host and virus factors. Fungi and oomycetes contain virus-like particles that do not obviously affect their hosts, for example, some plant viroids and bacterial phages cause disease in only a subset of hosts or growth conditions (Flores *et al.,* 2005; Oppenheim *et al.,* 2005; Pearson *et al.,* 2009). Such agents may have caused strong symptoms at some point, but evolutionary pressures probably diminished their effects and in some cases caused shifts to mutualisms, (Judelson and Fabritius, 2000). Mycoviruses are of common occurrence in endophytic fungi (fungal endosymbionts of plants), with potentially mutualistic roles in the complex interactions between the two organisms (Bao and Roossinck, 2013; Herrero *et al*., 2009, 2011). It is important to note that several of these viruses are from endophytic fungi, thus they reside in fungal hosts which reside in plants.

Interaction of Mycoviruses with Host Fungi

Fungal viruses or mycoviruses can modify plant-fungal symbioses. Beneficial interactions involve environmental protection to the host plant, protection against other pathogens, or control of plant responses to nutritional needs (Roossinck, 2011). For example, mycoviruses might represent mobile elements that afford their partners greater flexibility for rapid adaptation, a promising trait during environmental changes**.** Another example, (Márquez *et al.,* 2007) reported a mutualistic association between a fungal endophyte (*Curvularia protuberata*) and a tropical panic grass (*Dichanthelium lanuginosum*) which allows both organisms to grow at high soil temperatures. The authors found that, fungal isolates cured of the virus are unable to confer heat tolerance, but heat tolerance is restored after the virus is reintroduced. However, their study in the field and laboratory experiments have shown that when root zones are heated up to 65°C, non-symbiotic plants either become shriveled and chlorotic or simply die, whereas symbiotic plants tolerate and survive the heat regime. When grown separately, neither the fungus nor the plant alone is able to grow at temperatures above 38 °C, but symbiotically, they are able to tolerate elevated temperatures. In the absence of heat stress, symbiotic plants have enhanced growth rate compared with nonsymbiotic plants and also show significant drought tolerance.

Moreover, (Judelson & Fabritius, 2000) in their previous study reported that PiERE1 did not noticeably alter the growth, sporulation, germination or pathogenic fitness of *P. infestans* . However, in their recent studies (Judelson *et al*., 2010) they reported that an RNA symbiont that was previously believed not to influence the biology of *P. infestans* does alter its growth. However, that PiERE1 exerts subtle effects on its host that aid growth at elevated temperatures, enhance secondary homothallism, and promote the survival of *P. infestans* in nature. These traits could be a consequence of cellular stress instigated by PiERE1, since the symbiont elevates the expression of several genes encoding the Hsp70 protein chaperone, which is a typical biomarker of heat stress. Also, (Vainio *et al*., 2012) reported a novel putative mycovirus Heterobasidion RNA virus 6 (HetRV6) on *Heterobasidion annosum* sensu lato. The HetRV6 was also successfully transmitted between the three European species (*H. abietinum*, *H. annosum* and *H. parviporum*). Based on growth rate tests on agar plates and spruce stem pieces, HetRV6 seemed to be slightly mutualistic to its host. Also, (Ahn and Lee, 2001) reported another mutualistic interaction involving a dsRNA virus and the plant-pathogenic fungus *Nectria radicicola* where by eliminating the virus makes the strains completely lost virulence-related phenotypes, but when the virus was reintroduced by hyphal anastomosis to a virus cured strain marked with hygromycin resistance, resulted in the restoration of virulence-related phenotypes.

Hypovirulence of Mycoviruses.

Hypovirulence is a phenomenon where the virulence of fungal pathogens is decreased, even lost, due to mycovirus infection (Zhang *et al.,* 2009). Only few mycoviruses are known to cause phenotypic alterations to their fungal host including hypovirulence and debilitation (Nuss, 2010) and therefore, they can be used as biological control agents against fungal diseases. Hypovirulence was first reported in the chestnut blight, a destructive disease caused by *Cryphonectria parasitica* by Grente (Grente, 1965). The successful control of chestnut blight with hypovirulent strains of *C. parasitica* represented an alternative approach to biological control of fungal diseases other than with mycoparasites and antagonists (Anagnostakis, 1982;1998**).**

Hypovirulence of *Sclerotinia* spp: Hypovirulence has been reported to occur in many species of *Sclerotinia*. Some of the reports on dsRNA-associated hypovirulence in *S. sclerotiorum* and other plant pathogenic *Sclerotinia spp*. have appeared （Boland, 1992; Xie *et al.,* 2006). However, the reports of (Xie *et al.,* 2006) has presented convincing evidence for the association of a novel, well-characterized, potex-like mycovirus *Sclerotinia sclerotiorum* debilitation associated RNA virus (SsDRV) with hypovirulence in the debilitated strain Ep-1PN of *S. sclerotiorum.* Also, the ssDNA mycovirus *Sclerotinia sclerotiorum* hypovirulence associated DNA virus can be used to control rape *Sclerotinia* rot caused by *S. sclerotiorum* (Yu *et al*., 2013). Another report on hypovirulence *S. sclerotiorum* is that of novel virus that infects hypovirulent strain XG36-1 of plant fungal pathogen *Sclerotinia sclerotiorum* grew on PDA plate, developed abnormal colony morphology with few sclerotia and it was unable to induce lesions on detached leaves of rapeseed (Zhang *et al.,* 2009). Hypovirulence and its associated traits of strain XG36-1 could be mediated by a fungal virus. Further more, (Boland, 2004) reported hypovirulence occured in *S. sclerotiorum, S. minor*, and *S. homoeocarpa* and, to varying degrees, has been also associated with the presence of dsRNAs. Biological control has been demonstrated through applications of hypovirulent isolates to diseased plant tissues in controlled and field environments. In *S. minor*, disease severity was suppressed by more than 50%, and the number of sclerotia produced on treated diseased tissues was reduced by up to 90%. Also, *S. homoeocarpa*, biocontrol efficacies of up to 90% and 80% have been achieved in controlled and field environments, respectively, and were comparable with treatment with a fungicide. Single applications of the hypovirulent isolate Sh12B, containing a strain of the species Ophiostoma mitovirus 3a (OMV3a) were as effective as up to four applications of fungicide.

Moreover, Xueqiong *et al.* (2014) reported a novel partitivirus, *Sclerotinia sclerotiorum* partitivirus 1 from hypovirulent strain WF-1 (SsPV1/WF-1) which conferred hypovirulence on its natural plant-pathogenic fungal host, *Sclerotinia sclerotiorum* strain WF-1. Cellular organelles, including mitochondria,were severely damaged. Moreover, the authors reporetd that, introduction of purified SsPV1/WF-1 virions into strain KY-1 of *Botrytis cinerea* also resulted in reductions in virulence and mycelial growth and, unexpectedly, enhanced conidial production. However, virus infection suppressed hyphal growth of most germinating conidia of *B. cinerea* and was eventually lethal to infected hyphae, since very few new colonies could develop following germ tube formation. Zhong *et al*. (2016) reported another hypovirulence of *Sclerotinia* from dsRNAs isolated from a debilitated *S. rolfsii* strain, BLH-1, which had pronounced phenotypic aberrations including reduced pathogenicity, mycelial growth and deficient sclerotia production. Also, virus-curing and horizontal transmission experiments that eliminated or transmitted, respectively, all dsRNA elements showed that the dsRNAs were involved in the hypovirulent traits of BLH-1. Ultrastructure examination also showed hyphae fracture and cytoplasm or organelle degeneration in BLH-1 hyphal cells compared to the virus-free strain. Moreover, Marzano *et al*. (2015) reported that *Sclerotinia sclerotiorum* isolate 328 was coinfected with a strain of *Sclerotinia sclerotiorum* endornavirus 1 and was debilitated compared to cultures of the same isolate that had been cured of virus infection by cycloheximide treatment and hyphal tipping. Also, to determine whether SsHV2L alone could induce hypovirulence in *S. sclerotiorum*, the authors cloned a full-length cDNA of the 14,538-nt viral genome and transcripts corresponding to the viral RNA were synthesized in vitro and transfected into a virus-free isolate of *S. sclerotiorum*, DK3. Also, the authors reported that, isolate DK3 transfected with *Sclerotinia sclerotiorum* hypovirus 2 Lactuca (SsHV2L) was hypovirulent on soybean and lettuce and exhibited delayed maturation of sclerotia relative to virus-free DK3, completing Koch's postulates for the association of hypovirulence with SsHV2L. Moreover, Yang *et al.* (2018) reported that *Sclerotinia minor* Endornavirus 1(SmEV1) in hypovirulent strain LC22 which have a protective activity against attack by *S. minor.* Castro *et al.,* (2003) reported another hypovirulence on *Botrytis cinerea* where by they performed virulence bioassays by direct plug mycelial inoculation on bean plant leaves, and the result showed that *B. cinerea* CCg425 displays less fungal aggressivity than *B. cinerea* CKg54, a virulent fungal strain that is not infected by dsRNA mycoviruses. Moreover, *B. cinerea* CCg425 also showed lower laccase activity and conidiation rate than *B. cinerea* CKg54. But when *B. cinerea* CKg54 was infected with viral particles purified from *B. cinerea* CCg425, it resulted in diminished virulence of the infected fungus.

Hypovirulence of *Botrytis species*: *Botrytis cinerea* RNA virus 1 (BcRV1) was found to be positively correlated with hypovirulence in *B. cinerea*, with the attenuation effects of BcRV1 on mycelial growth and pathogenicity being greatly affected by the accumulation level of BcRV1 (Lin *et al.,* 2015). The authors reported that strains with BcRV1 are severely attenuated in pathogenicity, causing leaf lesions with severely attenuated in mycelial growth and formed abnormal colonies with sectored colony margin. BcRV1 can be transmitted vertically through asexual spore macroconidia and horizontally to other strains of *B. cinerea* through hyphal contact. The BcRV1 accumulation level greatly affects the attenuation effect of BcRV1 on the pathogenicity of *B. cinerea*. Also, Fangmin *et. al.* (2018) reported that infection by *Botrytis cinerea* hypovirus 1(BcHV1) alone caused attenuated virulence without affecting mycelial growth, significantly inhibited infection cushion (IC) formation, and altered expression of several IC-formation-associated genes. The authors added that, wound inoculation could fully rescue the virulence phenotype of the BcHV1 infected isolate. These results indicate the BcHV1-associated hypovirulence is caused by the viral influence on IC-formation associated pathways.

Further more, Lifeng *et al.* (2016) reported that a novel double-stranded RNA (dsRNA) virus, designated as *Botryosphaeria dothidea* RNA virus 1 (BdRV1), isolated from a hypovirulent strain YZN115 of *Botryosphaeria dothidea*. BdRV1 conferred hypovirulence for its host and could be transmitted through conidia and hyphae contact via asexual sporulation at 100% rate strain JNT1111, derivatives Y15-J111-1, Y15-J111-2, and Y15-J111-3 infected by BdRV1 showed slow growth speed and their colony margins were sectored, and even did not produce any pycnidium after incubation for 60 days. These results revealed that the impaired growth rates were correlated with transmission of BdRV1. The results shows that, sub-strains Y15-J111-1, Y15-J111-2, and Y15-J111-3 did not cause disease lesions, but strain JNT1111 caused large black cankers on the shoots of pear and apple fruits at 5 dpi. Furthermore, Wu et al. (2007) tested that twenty-one strains of *Botrytis cinerea* on *Brassica napus*.The results showed that the strain CanBc-1 was severely debilitated in pathogenicity and mycelial growth, compared with the 20 virulent strains.

Hypovirulence in *Fusarium* spp. : Several mycoviruses have been reported worldwide from *Fusarium species* but only a minimal number of mycoviruses cause hypovirulence in *Fusarium* (Gupta, 1991) the recent reports were; *Fusarium graminearum* virus 1 (FgV1) which was the first Fusarium mycovirus to be characterized. It led to the decreased pathogenicity of fungus and morphological variations, including increased pigmentation and lesser mycelial growth (Yu *et al.,* 2015). However, It has been seen that if mango is inoculated with a VLP-infected and VLP-free isolate of *Fusarium moniliforme*, only the VLP-free isolate caused shoot malformation. This suggests that the mycovirus contained in *F. moniliforme* may be responsible for suppressing mango shoot malformation. Moreover, Aminian *et al.* (2011) detected three different dsRNAs, of 0.9–5 kbp in size, from twelve *F. graminearum* isolates of wheat in Iran. The dsRNAs of those twelve isolates caused less serious disease than dsRNA-free isolates and developed substantially less quantities of the mycotoxin deoxynivalenol (DON) on susceptible wheat in the greenhouse. However, Li *et al.* (2015) reported that *Fusarium graminearum* Hypovirus 2 (FgHV2/JS16) was shown to be associated with hypovirulence phenotypes according to comparisons of the biological properties shared between FgHV2/JS16-infected and FgHV2/JS16-free isogenic strains. Demonstrated that, infection of FgHV2/JS16 activated the pathway of RNA interference in *F. graminearum* by relative quantitative real-time RT-PCR.

Hypovirulence of *Penicillium species*: Another report on hypovirulence of mycovirus was reported by (Nui *et al.*, 2018). The authors reported two novel mycoviruses *Penicillium digitatum* polymycovirus 1 (PdPmV1) and *Penicillium digitatum* Narna-like virus 1 (PdNLV1), coexisting in *P. digitatum* strain HS-RH2.The fungicide-resistant P. digitatum strains HS-F6 and HS-E9 coinfected by PdPmV1 and PdNLV1 and the results revealed that mycovirus-induced reduction of fungicide resistance.

Hypovirulence of *Rhizoctonia solani*: Zheng *et al.* (2014) reported a mycovirus *Rhizoctonia solani* partitivirus 2 (RsPV2) from strain GD-11 of *R. solani* AG-1 IA, the causal agent of rice sheath blight. The authors reported that, introduction of purified RsPV2 virus particles into protoplasts of a virus-free virulent strain GD-118 of *R. solani* AG-1 IA resulted in a derivative isogenic strain GD-118T with reduced mycelial growth and hypovirulence to rice leaves. Hence, the authors concluded that RsPV2 is a novel dsRNA virus belonging to Alphapartitivirus, with potential role in biological control of *R. solani.*

CONCLUSION

The findings we have outlined here showed that, hypovirulent mycoviruses are widespread in major fungi genera, but mostly reported in *Sclerotinia* than in any other fungal genus. Eventhough, their mode of isolation from host fungi and their mode of application to the host plants are still unknown, further researches may uncover the relationship between infected fungi and host plant, mode of transmissions of mycoviruses in to the host plants and their detrimental effects in the plant cells which are hosts for the fungi. This is beecause viruses infecting fungal endophytes must also have relationship with the plant cells which are hosts for the fungi. These informations will be essential to develop a durable, cost effective and sustainable strategy for the management of plant pathogenic fungi, alternative to use of synthetic pesticides. Also, may eventually provide an avenue for commercial production of these hypovirulence mycoviruses and make them available to farmers.

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