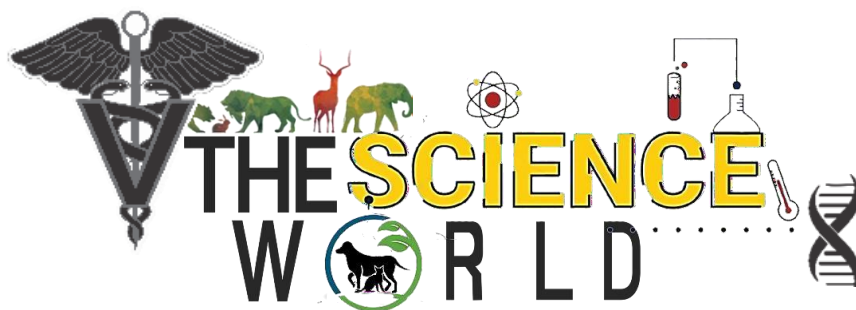




A Monthly e Magazine
ISSN:2583-2212

Popular Article

Oct, 2026 Vol.6(10), 3142-3147

Mycoviruses: Could Viruses Be Used to Control Fungal Diseases?

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doi.org/10.5281/ScienceWorld.23337323

Abstract

Fungal diseases cause substantial losses in agriculture and can also cause serious disease in animals and humans. The emergence of antifungal resistance and the limitations of conventional antifungal drugs have increased interest in alternative approaches to fungal disease management. Mycoviruses, viruses that infect fungi, offer an unusual possibility because some can alter fungal growth, reproduction, metabolism, toxin production, and virulence. When a mycovirus reduces the disease-causing ability of its fungal host, the phenomenon is known as hypovirulence. The classic example is *Cryphonectria hypovirus 1* (CHV-1), which reduces the virulence of the chestnut blight fungus *Cryphonectria parasitica*. Research has since identified mycoviruses in many fungal groups, including human-pathogenic fungi. Although mycoviruses show promise as biological control agents, practical application is limited by challenges involving transmission, host compatibility, delivery, stability, and field performance. Advances in next-generation sequencing, fungal molecular biology, and bioinformatics are rapidly expanding the discovery and study of these viruses. Mycoviruses therefore represent an emerging approach to sustainable fungal disease management, but considerable research is still required before they can become routine control tools.

Keywords: Mycovirus, hypovirulence, fungal disease, biological control, antifungal resistance, fungal pathogens, mycovirology

Introduction

Fungal diseases are an important challenge in agriculture, veterinary medicine, and human health. Fungi such as *Aspergillus*, *Candida*, *Cryptococcus*, *Fusarium*, and members of the Mucorales can cause serious infections, particularly in immunocompromised individuals. The problem is further complicated by resistance to commonly used antifungal agents and by the adverse effects associated with some antifungal drugs (Enoch *et al.*, 2006; Snelders *et al.*, 2008).



Interestingly, fungi themselves can become infected with viruses. These viruses are known as mycoviruses. Most mycoviruses have little or no obvious effect on their fungal hosts, but some can profoundly alter fungal biology. In particular, certain mycoviruses can reduce the virulence of their fungal hosts, a phenomenon known as hypovirulence (Kotta-Loizou, 2021; Hough *et al.*, 2023).

This unusual relationship between viruses and fungi raises an intriguing question: instead of directly killing a fungal pathogen with an antifungal agent, could a virus be used to weaken the fungus from within?

What are mycoviruses?

Mycoviruses are viruses that infect fungi. Early observations of fungal viruses date back to the 1960s, when viral infections were reported in fungi including the cultivated mushroom *Agaricus bisporus* and *Penicillium* species. Interest in mycovirolgy expanded substantially with the study of hypovirulence in the chestnut blight fungus *Cryphonectria parasitica*.

Cryphonectria hypovirus 1 (CHV-1) became a landmark example because infection reduces the virulence of *C. parasitica*. The infected fungus becomes less capable of causing severe disease in chestnut trees, providing a classic demonstration of virus-mediated fungal hypovirulence (MacDonald and Fulbright, 1991). Since then, mycoviruses have been detected in a wide range of fungi, including filamentous fungi and yeasts. Their genomes are diverse, with RNA genomes predominating, and modern sequencing technologies have greatly accelerated the discovery of previously unknown fungal viruses (Hough *et al.*, 2023).

How can a virus help control a fungus?

At first glance, using a virus to control a fungus may seem unusual. However, mycoviruses can influence several biological characteristics of their fungal hosts. Depending on the particular virus and fungal strain, infection may be associated with reduced fungal growth, changes in biomass, altered colony morphology or pigmentation, reduced or altered sporulation, changes in reproductive capacity, altered metabolism, changes in toxin production, and reduced pathogenicity or virulence (Kotta-Loizou, 2021; Hough *et al.*, 2023).

When mycovirus infection reduces the disease-causing ability of a fungal host, this is known as hypovirulence. The interaction between CHV-1 and *C. parasitica* remains one of the best-known examples of how a naturally occurring mycovirus can weaken a fungal pathogen. This discovery stimulated research into the use of mycoviruses as biological control agents against other fungal diseases (MacDonald and Fulbright, 1991; García-Pedrajas *et al.*, 2019).



Mycoviruses as biological control agents

The potential of mycoviruses is particularly interesting in plant disease management. Several mycoviruses associated with hypovirulence have been investigated against important fungal pathogens. Examples include *Sclerotinia sclerotiorum* hypovirulence-associated DNA virus 1 (SsHADV-1), which has been studied for its ability to reduce the virulence of *Sclerotinia sclerotiorum*, and *Rosellinia necatrix* megabirnavirus 1 (RnMBV1), associated with the white root rot fungus *Rosellinia necatrix* (Chiba *et al.*, 2009; Yu *et al.*, 2010).

The concept is simple but powerful: natural enemies of fungal pathogens may themselves become tools for disease management. However, successful biological control depends on more than the ability of a virus to reduce fungal virulence. The virus must also be able to move efficiently through the target fungal population. Transmission efficiency, fungal compatibility, environmental conditions, and disease biology all influence the success of a mycovirus-based strategy (García-Pedrajas *et al.*, 2019).

How do mycoviruses spread?

One of the most interesting features of mycoviruses is their method of transmission. Most mycoviruses do not have a conventional extracellular transmission route. Instead, they are commonly transmitted through the fungal cytoplasm. Hyphal anastomosis, in which compatible fungal hyphae fuse and exchange cytoplasmic contents, is an important mechanism of horizontal transmission. Mycoviruses may also be transmitted vertically through fungal reproductive structures such as conidia and ascospores, allowing a virus to move from an infected fungal parent to its progeny (García-Pedrajas *et al.*, 2019; Hough *et al.*, 2023).

This biology creates an important practical challenge. When genetically incompatible fungal strains encounter each other, cellular defence mechanisms can prevent successful viral transmission. Consequently, a mycovirus that performs well in the laboratory may not spread efficiently through a genetically diverse fungal population in the field.

How are mycoviruses detected?

The discovery of mycoviruses has traditionally involved the detection of viral double-stranded RNA in fungal cultures. Purification of dsRNA followed by agarose gel electrophoresis has been an important classical approach. However, conventional methods have limitations. Low viral titres may result in false-negative findings, while methods specifically targeting dsRNA may fail to detect DNA viruses.

Modern next-generation sequencing (NGS) has transformed mycovirus research. Metagenomic and metatranscriptomic approaches can identify viral sequences directly from large



datasets without requiring prior knowledge of the virus. Researchers commonly search for conserved viral genes, particularly those encoding RNA-dependent RNA polymerase (RdRp), an important enzyme in RNA virus replication. The availability of fungal genomic and transcriptomic datasets has therefore made it possible to explore mycovirus diversity in fungal species that were previously difficult to investigate (Hough *et al.*, 2023).

From laboratory discovery to field application

Finding a mycovirus is only the beginning. For a mycovirus to become a practical biological control agent, researchers need to demonstrate that it consistently reduces the pathogenicity or fitness of the target fungus and that the effect can be maintained under relevant conditions.

A general development pathway can be represented as:

Identification → isolation and characterisation → generation of virus-infected and virus-free fungal strains → confirmation of hypovirulence → transmission studies → stability testing → development of delivery methods → field evaluation.

The virus-infected fungal strain can then be compared with an appropriate virus-free strain to determine whether observed changes are associated with viral infection. Efficient transmission is particularly important. A mycovirus that strongly reduces fungal virulence but cannot spread efficiently through a fungal population may have limited value as a biological control agent (García-Pedrajas *et al.*, 2019).

Challenges ahead

Despite its promise, mycovirus-based disease management remains an emerging field. Several challenges must be addressed before widespread application becomes possible. First, efficient delivery is difficult because most mycoviruses remain within fungal cells and lack a conventional extracellular transmission mechanism. Second, vegetative incompatibility between fungal strains can restrict horizontal transmission. Third, the virus must remain stable and biologically effective under environmental conditions encountered by the target pathogen. Fourth, host specificity must be carefully evaluated because unintended effects on beneficial or non-target fungi should be avoided.

Laboratory observations also do not necessarily predict field performance. Temperature, humidity, host plants, competing microorganisms, and pathogen population structure can all influence virus-fungus interactions. Finally, a successful laboratory isolate must eventually be converted into a practical formulation and delivery system that can be produced, stored, and applied economically. These challenges explain why mycoviruses should currently be viewed as



an emerging biological control strategy rather than an immediate replacement for conventional antifungal agents (García-Pedrajas *et al.*, 2019; Hough *et al.*, 2023).

Future prospects

The field of mycovirology is gradually moving from simply discovering fungal viruses to understanding how their biological effects can be harnessed. Advances in next-generation sequencing, fungal genetics, molecular biology, and bioinformatics are making it easier to discover new mycoviruses and investigate their interactions with fungal hosts.

Future research may focus on identifying naturally occurring hypovirulence-associated viruses, understanding the molecular basis of hypovirulence, improving viral transmission, and developing effective delivery systems. Another important area will be understanding the ecological relationship between fungi, mycoviruses, and their environment, because the effects of a mycovirus may depend on both fungal genotype and environmental conditions (Kotta-Loizou, 2021).

The ultimate goal is to convert naturally occurring fungus-virus interactions into safe, reliable, and practical tools for fungal disease management.

Conclusion

Fungal pathogens have traditionally been controlled using chemical antifungal agents and fungicides. However, increasing resistance, treatment limitations, and the emergence of difficult-to-control fungal pathogens highlight the need for alternative strategies.

Mycoviruses offer a different way of thinking about fungal disease control. Instead of directly destroying the fungus, a suitable mycovirus may weaken it, reduce its reproduction, alter its metabolism, or decrease its ability to cause disease. The journey from discovering a mycovirus to developing a practical biological control agent is complex, and many scientific questions remain unanswered.

Nevertheless, the study of mycoviruses has opened an intriguing research area connecting virology, mycology, molecular biology, and biological control. The future may therefore bring an unusual but scientifically promising approach to fungal disease management: using a fungus's own viruses against the fungus itself.

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