Mycophenolic acid has antiviral activity against different influenza virus subtypes affecting humans

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OBJECTIVE:

There is an increasing number of influenza virus isolates that are resistant to neuraminidase inhibitors. Repurposing of approved drugs is an attractive option to reduce the time and cost of finding novel anti-influenza drugs. Using a high-throughput chemical screening platform, we have previously shown that mycophenolic acid (MPA) has anti-influenza activity [1]. MPA is a non-competitive reversible inhibitor of inosine monophosphate dehydrogenase leading to guanosine depletion, and has been used in the prevention of graft rejection in transplant recipients and in the treatment of autoimmune diseases. In this study, we sought to evaluate the antiviral activity of MPA against the influenza A(H1N1) and A(H7N9) virus affecting humans.

METHODS

Influenza A(H1N1) and A(H7N9) virus strains used in this study were isolated from patients. The antiviral activity of MPA against influenza viruses were evaluated using cell protection assay, virus yield reduction assay and plaque reduction assay in Madin Darby canine kidney cells. Reversal of antiviral activity by the addition of guanosine or adenosine was also performed.

Table 1. Antiviral activity of mycophenolic acid against influenza virus

Influenza virus subtype	Virus strain	Plaque reduction assay IC_{50} (μM)
A(H1N1)	A/Hong Kong/415742/2009	0.624
	A/Hong Kong/402467/2014	0.344
A(H7N9)	A/Anhui/1/2013	0.872
	A/Zhejiang/DTID-ZJU01/2013	0.919

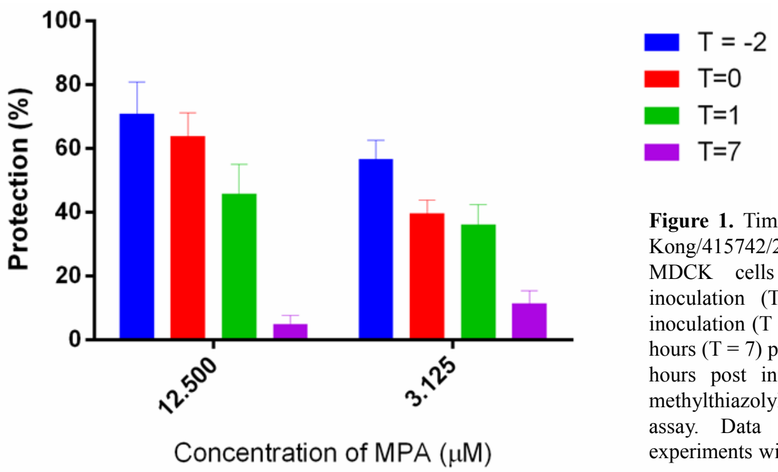
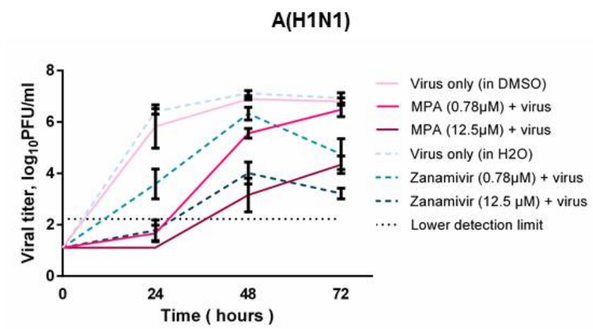


Figure 1. Time-of-addition assay for A/Hong Kong/415742/2009. MPA was added to the MDCK cells at 2 hours before virus inoculation (T= -2), at the time of virus inoculation (T = 0), or at 1 hour (T = 1) and 7 hours (T = 7) post infection. Cell viability at 72 hours post infection was determined using methylthiazolyldiphenyl-tetrazolium bromide assay. Data represents the mean of 3 experiments with duplicate in each experiment.



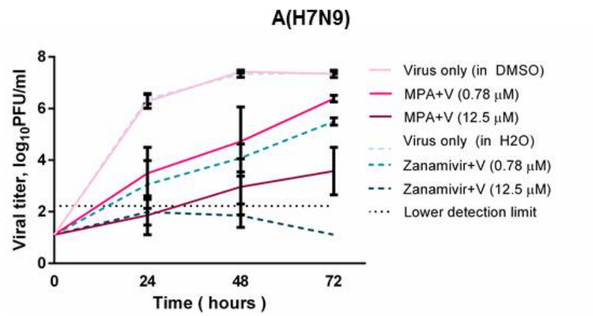


Figure 2. Antiviral activity of MPA using virus yield reduction assay

RESULTS

MPA protected cells from virus-induced cytotoxicity when added 2 hours before or added at the time of virus infection (% of viable cells >50%). However, cell protection was significantly lower when MPA was added 7 hours post-infection (% of viable cells <10%) (Figure 1). Using plaque reduction assay in which MPA was added 2 hours before virus infection, the IC50 was similar for A(H1N1) and A(H7N9) virus (Table 1). Virus yield reduction assay also showed that MPA inhibited virus replication (Figure 2). Addition of guanosine almost completely reverted the antiviral activity of MPA, while the addition of adenosine did not (Figure 3).

CONCLUSION:

MPA is a potent antiviral against influenza viruses affecting humans, including avian-origin A(H7N9) virus. Depletion of guanosine is the likely mechanism for the antiviral effect.

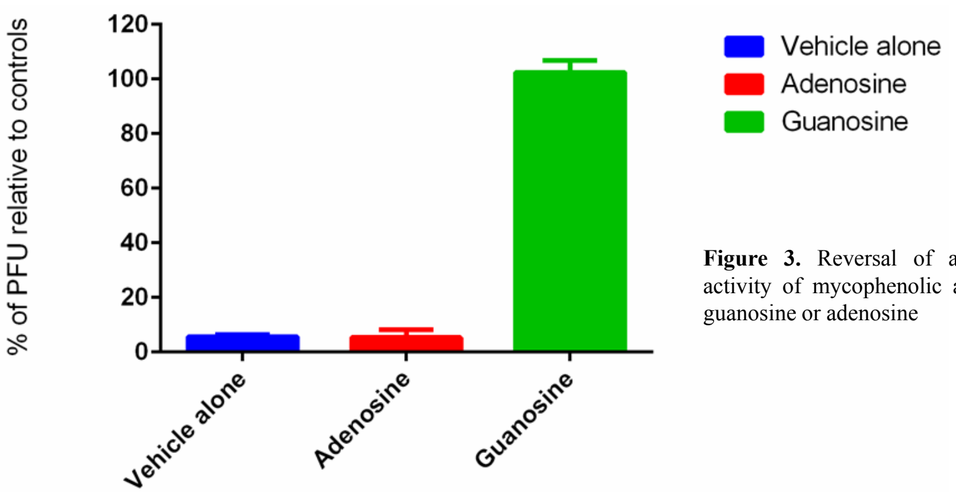


Figure 3. Reversal of antiviral activity of mycophenolic acid by guanosine or adenosine

REFERENCE1. Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, Li PT, Dai J, Mok FK, Chen H, et al.: **Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus**. *J Infect* 2013, **67**:606-616.