Tropical Biomedicine 38(3): 239-247 (2021)
https://doi.org/10.47665/tb.38.3.063

RESEARCH ARTICLE

In vitro antiviral activity of medicinal mushroom *Ganoderma neo-japonicum* Imazeki against enteroviruses that caused hand, foot and mouth disease

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ARTICLE HISTORY

Received: 16 April 2021
Revised: 29 May 2021
Accepted: 30 May 2021
Published: 31 July 2021

ABSTRACT

Hand, foot and mouth disease (HFMD) is a highly contagious viral disease that predominantly affects children younger than 5 years old. HFMD is primarily caused by enterovirus A71 (EV-A71) and coxsackievirus A16 (CV-A16). However, coxsackievirus A10 (CV-A10) and coxsackievirus A6 (CV-A6) are being increasingly reported as the predominant causative of HFMD outbreaks worldwide since the past decade. To date, there are still no licensed multivalent vaccines or antiviral drugs targeting enteroviruses that cause HFMD, despite HFMD outbreaks are still being frequently reported, especially in Asia-Pacific countries. The high rate of transmission, morbidity and potential neurological complications of HFMD is indeed making the development of broad-spectrum antiviral drugs/agents against these enteroviruses a compelling need. In this study, we have investigated the *in vitro* antiviral effect of 4 *Ganoderma neo-japonicum* Imazeki (GNJI) crude extracts (S1-S4) against EV-A71, CV-A16, CV-A10 and CV-A6. GNJI is a medicinal mushroom that can be found growing saprophytically on decaying bamboo clumps in Malaysian forests. The antiviral effects of this medicinal mushroom were determined using cytopathic inhibition and virus titration assays. The S2 (1.25 mg/ml) hot aqueous extract demonstrated the highest broad-spectrum antiviral activity against all tested enteroviruses in human primary oral fibroblast cells. Replication of EV-A71, CV-A16 and CV-A10 were effectively inhibited at 2 hours post-infection (hpi) to 72 hpi, except for CV-A6 which was only at 2 hpi. S2 also has virucidal activity against EV-A71. Polysaccharides isolated and purified from crude hot aqueous extract demonstrated similar antiviral activity as S2, suggesting that polysaccharides could be one of the active compounds responsible for the antiviral activity shown by S2. To our knowledge, this study demonstrates for the first time the ability of GNJI to inhibit enterovirus infection and replication. Thus, GNJI is potential to be further developed as an antiviral agent against enteroviruses that caused HFMD.

Keywords: Antiviral; enteroviruses; *Ganoderma neo-japonicum* Imazeki; hand, foot and mouth disease.

INTRODUCTION

Hand, foot and mouth disease (HFMD) is a common pediatric infectious disease caused by Enterovirus A species (EV-A) within the family of *Picornaviridae*. Enteroviruses are non-enveloped and positive-sense single-stranded RNA viruses (Linden *et al*., 2015). Enterovirus A71 (EV-A71) and coxsackievirus A16 (CV-A16) are the most prevalent etiological pathogens for HFMD (Klein & Chong, 2015). However, CV-A10 and CV-A6 are rapidly emerging and being increasingly reported to cause HFMD outbreaks worldwide such as in Finland (Blomqvist *et al*., 2010), Taiwan (Wei *et al*., 2011), Spain (Bracho *et al*., 2011), France (Mirand *et al*., 2012), Edinburgh in the United Kingdom (Stewart *et al*., 2013), China (Chen *et al*., 2017; Bian *et al*., 2019), Vietnam (Anh *et al*., 2018), Argentina (Cisterna *et al*., 2019), Belem in Northern Brazil (Justino *et al*., 2020) and Uruguay (Lizasoain *et al*., 2020). Children under the age of 5 are the most susceptible and vulnerable groups for HFMD. Although rare, infections with EV-A71 can be associated with severe central nervous system (CNS) complications (Lei *et al*., 2015). In contrast, CV-A16, CV-A10 and CV-A6 associated HFMD are usually self-limited with symptoms such as fever, mouth ulcers and skin rashes on palms and/or soles of the feet (Repass *et al*., 2014). HFMD is highly contagious and easily transmitted from person-to-person via oral-oral and/or fecal-oral routes (Klein & Chong,