Commentary: Combination Treatment Using Favipiravir for Crimean-Congo Hemorrhagic Fever

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Abstract

Crimean-Congo hemorrhagic fever virus is a tick-borne bunyavirus that causes Crimean-Congo hemorrhagic fever, characterized by acute febrile illness and rapid progress to severe hemorrhage manifestations with a high mortality rate. No specific antiviral drugs have been approved for the treatment of Crimean-Congo hemorrhagic fever. Favipiravir, a broad-spectrum antiviral drug originally developed for influenza, is known to inhibit the activity of RNA-dependent RNA polymerase of various RNA viruses. Recently, favipiravir demonstrated *in vivo* efficacy against Crimean-Congo hemorrhagic fever virus in animal models. For the purpose of promptly finding effective drugs for Crimean-Congo hemorrhagic fever, drug repurposing has been proposed. Especially, computational screening through *in silico* studies offer a cost-effective and time-efficient approach to identifying potential drug candidates for repurposing. This approach demonstrated that tetracycline and the phytochemical skullcapflavone I, are efficacious against Crimean-Congo hemorrhagic fever virus. *Scutellaria*, which contains skullcapflavone I in its extracts, is a component of the Kampo medicines

Sho-saiko-to and Saiko-keishi-to. In the near future, the aforementioned drugs may be recognized as Crimean-Congo hemorrhagic fever virus inhibitors. Furthermore, considering the synergistic effects of drugs, a combination of favipiravir and tetracycline, or a combination of favipiravir and Kampo medicine may be more effective.

Keywords: Crimean-Congo hemorrhagic fever virus, favipiravir, tetracycline, Kampo medicine

Crimean-Congo hemorrhagic fever virus (CCHFV) is an emerging tick-borne virus that causes CCHF, characterized by acute febrile illness and rapid progress to severe hemorrhage manifestations with a high mortality rate ranging from 30% to 50% in humans [1]. It extends across vast regions of Africa, Asia, Eastern Europe, and the Middle East. CCHFV belongs to the *Nairovirus* genus of the *Bunyaviridae* family, which is an enveloped virus with a tri-segmented negative-sense, single-stranded RNA genome, comprising small (S), medium (M), and large (L) segments. The L segment encodes the RNA-dependent RNA polymerase (RdRp) associated with viral RNA replication. This enzyme is multifunctional and includes a cap-dependent endonuclease domain, which plays a critical role in viral transcription through a process called cap-snatching, wherein the host mRNAs are cleaved near their 5’ cap structures. The capped RNA fragments are subsequently used as primers by the viral RdRp to synthesize viral mRNAs. The M segment encodes the envelope glycoprotein, which facilitates host cell entry and mediates virion maturation and assembly. The S

segment, a small genome part, encodes a nucleoprotein (NP) that plays a pivotal role in the viral lifecycle by binding to the viral genomic RNA and forming ribonucleoprotein complexes. These complexes are crucial for viral replication and packaging.

No specific antiviral drugs, including ribavirin, have been approved for the treatment of CCHF. Favipiravir (FAV), a broad-spectrum antiviral drug originally developed for influenza, is known to inhibit the activity of RdRp of various RNA viruses. Recently, FAV demonstrated *in vivo* efficacy against CCHFV in animal models. In this study, it reduced viral load and improved survival when administered shortly after infection [1]. Dülger et al. reported a 65-year-old man diagnosed with both COVID-19 and CCHF, who was treated with FAV 1600 mg twice on the first day, and 600 mg twice a day for the following 4 days. Five days after starting FAV treatment, his clinical symptoms and laboratory parameters normalized. They concluded that FAV might be effective for CCHF as well as COVID-19 [2].

Recent studies have shown that the CCHFV NP, a crucial protein in viral replication, may be considered a potential target for antiviral drug discovery strategies. Recently, it was demonstrated that a high-affinity small protein, known as Affimer, specifically binds to the CCHFV NP, thereby blocking viral RNA interaction and inhibiting viral replication using a mini-genome system [3].

For the purpose of promptly finding effective drugs for CCHF, drug repurposing has been proposed. Especially, computational screening through *in silico* studies offer a cost-effective and time-efficient approach to identifying potential drug candidates for repurposing. This approach demonstrated that

tetracyclines, such as doxycycline and minocycline, bind to the CCHFV NP and disrupt the interaction between viral RNA and NP, likely inhibiting CCHFV replication [4]. Thereafter, Hirano et al. demonstrated that tigecycline, another tetracycline, disrupted the interaction between CCHFV NP and viral RNA *in vitro* [5]. Given their antiviral and anti-inflammatory effects, tetracyclines have already been prescribed or proposed for various viral infections, such as COVID-19, influenza and Mpox [6－9]. These findings suggest that tetracyclines may be similarly efficacious against CCHFV. Another *in silico* study on phytochemicals demonstrated that skullcapflavone I, niazirin, and withanolide E have binding affinities with the CCHFV NP [10]. *Scutellaria*, which contains skullcapflavone I in its extracts, is a component of the Kampo medicines (KMs) Sho-saiko-to, Saiko-keishi-to, and others (Table 1). Kampo medicine is traditional Japanese medicine based on unique theories and therapeutic methods of traditional Chinese medicine. KMs primarily consist of organic plant-based ingredients, such as *Scutellaria*, *Ziziphus jujuba*, *Bupleurum*, *Glycyrrhiza*, and others (Table 1). Due to their antiviral and anti-inflammatory properties, Sho-saiko-to and Saiko-keishi-to have already been prescribed or proposed for the treatment of COVID-19, influenza and Mpox [6－9]. These findings suggest that aforementioned KMs may be similarly efficacious against CCHFV. There are approximately 150 types of KM that can be commercially prescribed in Japan. KMs are inexpensive and are routinely prescribed by clinicians in Japan for various conditions, including pulmonary diseases, hepatic diseases, urological diseases, menopausal disorders, and dementia. KM is covered under Japan's national health insurance

system; therefore, KM can be more affordable for patients. Moreover, KM is generally easy to take orally, as it comes in the form of powder-like granule.

Taken together, the aforementioned drugs may be recognized as CCHFV inhibitors in the near future. Furthermore, considering the synergistic effects of the drugs, a combination of FAV and tetracycline, or a combination of FAV and KM may be more effective. In any case, clinical trials are warranted to better assess the optimal doses and durations, as well as the efficacy and tolerability, before these treatments can be recommended on a wider basis.

Conflict of interest

The authors have no conflict of interest associated with this article.

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Japanese names in roman characters (Chinese name for Pinyin)	**ingredients and daily dosage (JP: The Japanese Pharmacopoeia)**
Kakkon-to (Ge Gen Tang)	JP *Pueraria* root 4.0 g, JP *Ziziphus jujuba* 3.0 g, JP *Ephedra* herb 3.0 g, JP *Glycyrrhiza* 2.0 g, JP *Cinnamon* bark 2.0 g, JP *Peony* root 2.0 g, JP *Ginger* 2.0 g
Sho-saiko-to (Xiao Chai Hu Tang)	JP *Bupleurum* root7.0 g, JP *Pinellia* tuber 5.0 g, JP *Scutellaria* root 3.0, JP *Ziziphus jujuba* 3.0 g, JP *Ginseng* 3.0 g, JP *Glycyrrhiza* 2.0, JP *Ginger* 1.0 g
Saiko-keishi-to (Chai Hu Gui Zhi Tang)	JP *Bupleurum* root 5.0 g, Pinellia tuber 4.0 g, JP *Scutellaria* root 2.0 g, JP *Glycyrrhiza* 2.0 g, JP *Cinnamon* bark 2.0 g, JP *Peony* root 2.0 g, JP *Ziziphus jujuba* 2.0 g, JP *Ginseng* 2.0 g, JP *Ginger* 1.0g

Mao-to (Ma Huang Tang)	JP *Apricot* kernel 5.0 g, JP *Ephedra* herb 5.0 g, JP *Cinnamon* bark 2.0 g, JP *Glycyrrhiza* 1.5 g
Sho-seiryu-to (Xiao Qing Long Tang)	JP *Pinellia* tuber 6.0 g, JP *Glycyrrhiza* 3.0 g, JP *Cinnamon* bark 3.0 g, JP *Schisandra* fruit 3.0 g, JP *Asiasarum* root 3.0 g, JP *Peony* root 3.0 g, JP *Ephedra* herb 3.0 g, JP *Processed Ginger* 3.0 g

Table 1