

Hypothesis

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Hypothesis

Drug Repurposing with Tetracycline and Kampo Medicine (Sho-Sai-Koto and Saiko-Keishi-to) for Crimean-Congo Hemorrhagic Fever: Predicting Efficacy Through In Silico Studies

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Abstract

The Crimean-Congo hemorrhagic fever virus is a tick-borne bunyavirus that leads to acute febrile illness with myalgia, dizziness, neck pain and headache and a high mortality rate in humans. Currently, no specific antiviral drugs have been approved for treatment, making the search for effective drugs against this virus and the execution of clinical trials a significant concern. Drug repurposing is a well-established strategy for redeploying existing licensed drugs for newer indications, facilitating the quickest transition from bench to bedside. Computational screening through in silico studies offer a cost-effective and time-efficient approach for identifying potential drug candidates for repurposing. This approach demonstrated that tetracyclines such as doxycycline and minocycline, along with 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 traditional Japanese medicines Shosaiko-to and Saiko-keishi-to (Kampo medicines). Kampo medicines are primarily formulated with organic plant-based ingredients and are known to have fewer adverse reactions compared to Western medicine. In the near future, the aforementioned drugs may be recognized as Crimean-Congo hemorrhagic fever virus inhibitors following in vitro and in vivo examinations.

Keywords: Crimean-Congo hemorrhagic fever virus; tetracycline; Kampo medicine

The Crimean-Congo hemorrhagic fever virus (CCHFV) is a tick-borne bunyavirus that causes acute febrile illness with myalgia, dizziness, neck pain and headache and is associated with a high mortality rate in humans. It extends across vast regions of Africa, Asia, the Middle East, and Southern Europe. 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 S segment encodes the nucleoprotein (NP). 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. This protein encapsulates the viral genome and forms a ribonucleoprotein complex, resulting in viral replication. Therefore, inhibition the binding between this protein and viral RNA impairs the replication. Currently, no specific antiviral drugs have been approved for the treatment of CCHFV infection. According to guidelines from the World Health Organization and the Centers for Disease Control and Prevention, treatment is limited to supportive care, including fluid balance control, hydration, fresh frozen plasma, appropriate therapy for secondary infection, and blood transfusions in hemorrhagic cases. Several reports discuss the use of type I interferon, immunoglobulin M antibodies, and ribavirin, but their efficacy is not supported by evidence [1]. Recently, a high-affinity small protein, known as Affimer, specifically binds to the CCHFV NP, thereby blocking viral RNA interaction and inhibiting viral replication in vitro in a mini-genome system [2]. Recent studies on CCHF indicate that vaccines targeting the GP38 glycoprotein

of the virus can protect mice from lethal infection, making it a strong candidate for future human vaccines [3]. The absence of an effective drug underscores the need to develop effective treatments against CCHFV and initiate clinical trials to assess their efficacy. Drug repurposing is a well-established strategy for redeploying existing licensed drugs for newer indications, enabling the shortest possible transition from the bench to the bedside. 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 [1]. Subsequently, Hirano et al. demonstrated that tigecycline, another tetracycline, disrupted the interaction between CCHFV NP and viral RNA *in vitro* [4]. 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 [5–8]. In another *in silico* study, Hashim et al. demonstrated that the beta-receptor blocker nebivolol and the antihistamine loratadine have the potential to bind to the RNA-binding region on the CCHFV NP and interfere with virus replication [9].

Furthermore, 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) Shosaiko-to and Saiko-keishi-to [7,11]. KM is a traditional Japanese medicine primarily consisting of organic plant-based ingredients, such as Scutellaria, Ziziphus jujuba, Bupleurum, Glycyrrhiza, and others [7]. Due to their antiviral and anti-inflammatory properties, Shosaiko-to and Saiko-keishi-to have already been prescribed for the treatment of COVID-19 and influenza in Japan [5–7]. These findings suggest that the two KMs may be efficacious against CCHFV. There are approximately 150 types of KM that can be commercially prescribed in Japan. KMs are low-priced and are routinely prescribed by clinicians in Japan for various diseases, including pulmonary diseases, hepatic diseases, urological diseases, menopausal disorders, dementia, and others. Moreover, they are known to cause fewer adverse reactions than Western medicines. Based on these results, the aforementioned drugs, particularly tetracyclines and KMs, may be recognized as CCHFV inhibitors in the near future, following *in vitro* and *in vivo* testing.

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

References

1. Sharifi A, Amanlou A, Moosavi-Movahedi F, Golestanian S, Amanlou M. Tetracyclines as a potential antiviral therapy against Crimean Congo hemorrhagic fever virus: Docking and molecular dynamic studies. *Computational Biology and Chemistry*. 2017 Oct 1;70:1-6.
2. Álvarez-Rodríguez B, Tiede C, Hoste AC, Surtees RA, Trinh CH, Slack GS, Chamberlain J, Hewson R, Fresco A, Sastre P, Tomlinson DC. Characterization and applications of a Crimean-Congo hemorrhagic fever virus nucleoprotein-specific Affimer: Inhibitory effects in viral replication and development of colorimetric diagnostic tests. *PLoS Neglected Tropical Diseases*. 2020 Jun 3;14(6):e0008364.
3. Golden JW, Shoemaker CJ, Lindquist ME, Zeng X, Daye SP, Williams JA, Liu J, Coffin KM, Olschner S, Flusin O, Altamura LA. GP38-targeting monoclonal antibodies protect adult mice against lethal Crimean-Congo hemorrhagic fever virus infection. *Science Advances*. 2019 Jul 10;5(7):eaaw9535.
4. Hirano M, Sakurai Y, Urata S, Kurosaki Y, Yasuda J, Yoshii K. A screen of FDA-approved drugs with minigenome identified tigecycline as an antiviral targeting nucleoprotein of Crimean-Congo hemorrhagic fever virus. *Antiviral Research*. 2022 Apr 1;200:105276.
5. Ohe M, Shida H, Yamamoto J, Seki M, Furuya K, Nishio S. COVID-19 Treated with Minocycline and Saiko-keishi-to: A Case Report. *International Med J*. 2024 Feb 1;31(1):27-8.
6. Ohe M, Shida H, Yamamoto J, Seki M, Furuya K. Successful treatment with minocycline and Saiko-keishi-to for COVID-19. *J Clin Exp Investig*. 2023;14(2):em00815.

7. Ohe M, Tsuchida N. Treatment with Kampo Medicine and Minocycline for Influenza. Preprints 2025, 2025011957. <https://doi.org/10.20944/preprints202501.1957.v1>
8. Ohe M. Drug Repurposing with Minocycline and Japanese Kampo Medicine for MPox: Predicting Efficacy Through In Silico Studies. International Med J. 2025 Mar 1;32(1):2-3.
9. Hashim AF, Odhar HA, Ahjel SW. Molecular docking and dynamics simulation analysis of nucleoprotein from the Crimea-Congo hemorrhagic fever virus strain Baghdad-12 with FDA approved drugs. Bioinformation. 2022 May 31;18(5):442.
10. Ramzan M, Mahmood S, Amjad A, Javed M, Zidan A, Bahadur A, Iqbal S, Saad M, Zaka N, Khurshid S, Awwad NS. Finding potential inhibitors from phytochemicals against nucleoprotein of Crimean-Congo fever virus using in silico approach. Scientific Reports. 2024 Dec 30;14(1):31804.
11. Park EJ, Zhao YZ, Lian L, Kim YC, Sohn DH. Skullcapflavone I from Scutellaria baicalensis induces apoptosis in activated rat hepatic stellate cells. Planta medica. 2005 Aug;71(09):885-7.

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