Hypothesis

Drug Repurposing with Minocycline and Japanese Kampo Medicine for MPox: Predicting Efficacy Through In Silico Studies

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Drug Repurposing with Minocycline and Japanese Kampo Medicine for MPox: Predicting Efficacy through In Silico Studies

Short title: Minocycline and Japanese Kampo Medicine for Mpox

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Abstract: Beginning in 2022, the Mpox outbreak, formerly known as monkeypox, has since spread to more than 100 countries and is now a global public health concern. This disease, caused by the Mpox virus, is usually mild, and most infected individuals recover within a few weeks without treatment. However, severe cases have been seen especially in children, pregnant women, or immunocompromised individuals. Antiviral medications such as brincidofovir, tecovirimat, and cidofovir were recently approved for Mpox; but these drugs are expensive and not easily obtainable. Therefore, identifying effective and low-cost drugs against Mpox and testing these through clinical trials remains a priority for global health. Drug repurposing is a well-known strategy for redeploying existing licensed drugs for newer indications, allowing for the shortest possible transition from bench to bedside. Recent *in silico* studies have determined the efficacy of minocycline, oleanolic acid, ursolic acid, and glycyrrhizinic acid against Mpox virus. Notably, oleanolic acid, ursolic acid, and glycyrrhizinic acid are some of the components of Japanese Kampo medicines, which are low-cost medicines prescribed daily in Japan. Thus, minocycline and Japanese Kampo medicines could potentially be used to treat Mpox.

Keywords: monkeypox; minocycline; Kampo medicine

In 2022, a global outbreak of Mpox, formerly known as monkeypox, occurred in various countries across Europe and America. After rapidly spreading to more than 100 countries, the outbreak has become a global public health concern. The disease is caused by the Mpox virus, which belongs to *Orthopoxvirus* genus. The variola virus, which causes smallpox, also belongs to this genus. The illness is usually mild, and most infected individuals recover within a few weeks without treatment. However, some cases may become severe, especially in children, pregnant women, or immunocompromised individuals.

Vaccination is recommended for those with a high risk of infection. An effective vaccine against Mpox has recently been developed, but it is not readily obtainable. Alternatively, smallpox vaccines have been found to provide 85% protection against Mpox [1]. Treatment is necessary for Mpox virus-infected individuals with severe disease or people who are immunocompromised, pediatric population, individuals with dermatitis or a prior history of it, and pregnant or breastfeeding women [2]. Brincidofovir and tecovirimat, which are antiviral medications approved by the United States Food and Drug Administration for smallpox, also have efficacy against Mpox due to the genetic resemblance of the two viruses [3]. Similarly, cidofovir, which has broad activity against Orthopoxviruses, was also found to be effective against Mpox [4]. However, these agents are expensive and not easily obtainable. Therefore, identifying effective and low-cost drugs against Mpox and testing these through clinical trials remains a priority for global health. Drug repurposing is a well-known strategy for redeploying existing licensed drugs for newer indications, allowing for the shortest possible transition from bench to bedside. In line with drug repurposing, minocycline (MIN) and Japanese Kampo medicines (e.g., Kakkon-to, Shosaiko-to-ka-kikyo-sekko, and Saiko-keishi-to) were successfully prescribed during the COVID-19 pandemic because of their effects against SARS-

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CoV-2 and their anti-inflammatory properties [5–8]. Kampo medicines are mainly created using organic plant-based ingredients, including JP *Ginseng*, JP *Glycyrrhiza*, JP *Ziziphus jujuba*, and others (Table 1) [5].

Table 1. Japanese Kampo medicine and Chinese medicine.

Japanese names in roman characters	Chinese name for Pinyin	ingredients and daily dosage (JP: The Japanese Pharmacopoeia)
Kakkon-to	Ge gen tang	JP Glycyrrhiza 2.0 g, JP Jujube 3.0 g, JP Pueraria Root 4.0 g, JP Ephedra Herb 3.0 g, JP Cinnamon Bark 2.0 g, JP Peony Root 2.0 g, JP Ginger 2.0 g
Shosaiko-to-ka-kikyo-sekko	Xiao chai hu tang jia jie geng shi gao	JP Ginseng 3.0 g, JP Glycyrrhiza 2.0, JP Jujube 3.0 g, JP Gypsum 10.0 g, JP Bupleurum Root 7.0 g, JP Pinellia Tuber 5.0 g, JP Scutellaria Root 3.0 g, JP Platycodon Root 3.0 g, JP Ginger 1.0 g
Saiko-keishi-to	Chai hu gui zhi tang	JP Ginseng 2.0 g, JP Glycyrrhiza 2.0 g, JP Jujube 2.0 g, JP Bupleurum Root 5.0 g, JP Pinellia Tuber4.0 g, JP Scutellaria Root 2.0 g, JP Cinnamon Bark 2.0 g, JP Peony Root 2.0 g, JP Ginger 1.0 g

Regarding drug repurposing for Mpox, an *in silico* study showed that tetracyclines possess potential inhibitory properties against the DNA-dependent RNA polymerase and viral core cystine proteinase of the Mpox virus [9]. Another *in silico* study demonstrated that oleanolic acid, a component of Shosaiko-to-ka-kikyo-sekko, and Saiko-keishi-to, and a *Ginseng* extract, has a strong binding affinity with the structural envelope proteins of the Mpox virus, thus showing promise as an inhibitor against the virus [10]. Similarly, ursolic acid, a component of Kakkon-to, Shosaiko-to-ka-kikyo-sekko, and Saiko-keishi-to, and a *Ziziphus jujuba* extract, was found to have the same property as oleanolic acid in another *in silico* study [10]. Lastly, glycyrrhizinic acid, a component of Kakkon-to, Shosaiko-to-ka-kikyo-sekko, and Saiko-keishi-to, and a *Glycyrrhiza* extract, was found to obstruct the DNA polymerase activity of the Mpox virus in an *in silico* study [11].

In cases wherein drugs have different mechanisms of action, multidrug treatment is more effective than single-drug therapy and has the added benefit of preventing the emergence of drug-resistant viruses. Therefore, treatment with MIN and Kakkon-to, and Shosaiko-to-ka-kikyo-sekko, or with MIN and Saiko-keishi-to, has potential in treating Mpox, similar to COVID-19 [6–8]. In any case, clinical trials are necessary to better assess the optimal doses and durations of these drugs, as well as their efficacy and tolerability before their widespread use.

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