Hypothesis

Treatment with Kampo Medicine and Minocycline for Influenza

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Treatment with Kampo Medicine and Minocycline for Influenza

Short Title: Kampo Medicine and Minocycline for Influenza

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Abstract: The main classes of antiviral drugs used to treat influenza are M2 inhibitors (e.g., amantadine), neuraminidase inhibitors (e.g., oseltamivir, zanamivir, and peramivir), and cap-dependent endonuclease inhibitors (e.g., baloxavir marboxil). Amantadine, a pioneering antiviral drug, was globally used for treating influenza. However, influenza A viruses have developed resistance to amantadine. Neuraminidase inhibitors are also at a risk of developing resistance. Combination treatments including these drugs have been successfully administered as new therapeutic approaches for addressing the issue of resistance. Kampo medicine, which is based on traditional Chinese medicine, is traditional Japanese medicine with unique theories and therapeutic methods. Kampo medicines including Mao-to, Kakkon-to, Sho-seiryu-to, Sho-saiko-to, and Saiko-keishi-to have been empirically used for treating influenza. Kampo medicines are mainly composed of organic plant-based ingredients. The ingredients used to make Kampo medicine include *Ephedra herb, Ziziphus jujuba, Glycyrrhiza, Bupleurum* root, and others, the extracts of which have demonstrated anti-influenza and/or anti-inflammatory activities. Recently, minocycline, a tetracycline, was also observed to exert anti-influenza virus activities. Multidrug treatment is more effective compared with single-drug treatment because of the synergistic effects of the different mechanisms of actions of the drugs involved. Therefore, we propose the combination of Kampo medicine and minocycline for treating influenza as an alternative to the above-mentioned conventional drugs and hope that this might resolve the issue of conventional drug-resistant influenza.

Keywords: influenza; Kampo medicine; minocycline

M2 inhibitors (e.g., amantadine), neuraminidase inhibitors (e.g., oseltamivir, zanamivir, and peramivir), and cap-dependent endonuclease inhibitors (e.g., baloxavir marboxil) are the main classes of antiviral drugs used to treat influenza. Amantadine was a pioneering antiviral drug that was globally used for treating influenza. However, influenza A viruses have developed resistance to amantadine. Consequently, physicians have stopped recommending amantadine as influenza therapy since 2006. Neuraminidase inhibitors, which have subsequently emerged as the primary antiviral drugs, are also facing the risk of resistance [1]. For addressing the issue of resistance, new therapeutic approaches that include multidrug treatments have been successfully practiced. Nguyen *et al*. demonstrated the synergistic anti-influenza activities of the triple combination of oseltamivir, amantadine, and ribavirin, which proved efficacious against multiple influenza virus strains *in vitro* [2]. Smee *et al*. also demonstrated the beneficial effects of the combination of favipiravir and oseltamivir on influenza A virus infections in mice [3].

Traditional Chinese medicine (TCM) uses a range of herbal formulae to treat influenza. Especially, Lianhua Qingwen (LHQW) capsule is recommended for treating influenza accompanied

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with headache, fever, sore throat, and other cold symptoms [4]. The components used to manufacture LHQW include *Ephedra* herb, *Glycyrrhiza*, and others [4]. Kampo medicine (KM) is traditional Japanese medicine based on unique theories and therapeutic methods of TCM. KMs including Mao-to, Kakkon-to, Sho-seiryu-to, Sho-saiko-to, and Saiko-keishi-to are reasonably priced and have been routinely prescribed by Japanese clinicians, for treating influenza or common cold since a long time [5]. Among the above-mentioned KMs, Mao-to and Kakkon-to have proved efficacious against influenza, when tested in vivo as well as in vitro [6]. The combination of Mao-to and Sho-saiko-to has been reported to be as effective as oseltamivir for treating influenza A infection in adults [7].

KM is mainly created using organic plant-based ingredients. The ingredients used to make KM include *Ephedra* herb, *Ziziphus jujuba*, *Glycyrrhiza*, *Bupleurum* root, etc (Table 1). *Ephedra* herb is one of the components of KM (e.g., Mao-to, Kakkon-to, and Sho-seiryu-to). Ephedrine, an *Ephedra* herb extract, inhibited the proliferation of influenza A virus and modulated inflammatory response *in vitro* [8]. *Ziziphus jujuba* is also one of the components of KM (e.g., Kakkon-to, Sho-saiko-to, and Saiko-keishi-to). Ursolic acid, a *Ziziphus jujuba* extract, repressed influenza A virus-triggered inflammation and oxidative stress in A549 cells [9]. Similarly, betulinic acid, which is also a *Ziziphus jujuba* extract, inhibited the proliferation of influenza virus in A549 cells. Furthermore, it decreased inflammatory cytokine levels such as interferon-μ, resulting in a rapid recovery from severe pulmonary inflammation in mice [10]. *Glycyrrhiza* is one of the components of KM (e.g., Mao-to, Kakkon-to, Sho-seiryu-to, Sho-saiko-to, and Saiko-keishi-to). Glycyrrhizin, a *Glycyrrhiza* extract, inhibited the uptake of the influenza A virus into the cell and pro-inflammatory molecules [11,12]. *Bupleurum* is one of the components of KM (e.g., Sho-saiko-to, and Saiko-keishi-to). Saikosaponin A, a *Bupleurum* extract, downregulated the NF-kB signaling pathway which is prerequisite for influenza virus infection of human cells, and pro-inflammatory cytokine production. In addition, during the early stage of innate immune responses following an influenza virus infection, saikosaponin A selectively decreased lung neutrophil and monocyte recruitment [13,14]. *Scutellaria* root is one of the components of KM (e.g., Sho-saiko-to, and Saiko-keishi-to). Wogonin, a *Scutellaria* extract, modulated 5′ adenosine monophosphate-activated protein kinase (AMPK) activation, thereby exhibiting antiviral activities against influenza [15]. *Ginseng* is one of the components of KM (e.g., Sho-saiko-to, and Saiko-keishi-to). A *Ginseng* extract exhibited inhibitory effects on the growth of influenza virus *in vitro* [16]. *Peony* root is one of the components of KM (e.g., Kakkon-to, Sho-seiryu-to, and Saiko-keishi-to). Benzoylpaeoniflorin and pentagalloylglucose, extracts of the *Peony* root, exhibited anti-influenza virus activity in neuraminidase inhibition assay [17]. KMs, due to their antiviral and anti-inflammatory activities, are preferred for rapid recovery from influenza-induced symptoms.

Table 1. Kampo medicine and Chinese medicine.

Japanese names in roman characters (Chinese name for Pinyin)	ingredients and daily dosage (JP: The Japanese Pharmacopoeia)
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
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-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
Sho-saiko-to (Xiao Chai Hu Tang)	JP Bupleurum root 7.0 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, 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 Giseng 2.0 g, JP Ginger 1.0 g

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Recently, minocycline (MIN), a tetracycline, was reported to hinder the export of viral ribonucleoproteins (vRNPs) from the nucleus, thereby inhibiting viral assembly and dissemination. Moreover, MIN further suppressed viral propagation by inhibiting influenza A virus-induced apoptosis [18].

Multidrug treatment is more effective than single-drug treatment because of the synergistic effects associated with the different mechanisms of action of the drugs concerned. Moreover, multidrug treatments might prevent the emergence of drug-resistant viruses. With regards to the combination of KM and MIN for treating viral infection, treatment with the combination of Saiko-keishi-to and MIN was reportedly effective for treating COVID-19 [19,20]. Based on these results, treatment with KMs and MIN, such as Kakkon-to, Sho-saiko-to and MIN, may be beneficial to patients with influenza, especially in case of infectious complications susceptible to MIN. Moreover, as an alternative to the above-mentioned conventional drugs, treatment with such combinations could resolve the issue of conventional drug-resistant influenza and shortage of conventional drugs.

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