Commentary

Treatment with Kampo medicine (Keigai-rengyo-to) and Minocycline for Respiratory syncytial virus infection

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Abstract

Respiratory syncytial virus (RSV) causes major global morbidity, yet effective antiviral treatments remain limited. Kampo medicines contain multiple plant-derived compounds—such as baicalin, glycyrrhizin, luteolin, quercetin, kaempferol, acteoside, phillyrin and rutin—that inhibit RSV replication, modulate interferon responses, and reduce inflammation in experimental models. Non-Kampo agents including minocycline and micafungin also show antiviral potential. Combining Kampo formulations, such as Keigai-rengyo-to, with minocycline may provide synergistic benefit. Repurposing these agents offers a practical strategy for developing RSV therapeutics, particularly for high-risk adults.

Keywords: Respiratory syncytial virus, Kampo medicine, minocycline

Respiratory syncytial virus (RSV) represents a substantial global health burden across all age groups. Worldwide, RSV is estimated to cause more than 30 million episodes of acute lower respiratory infection annually in young children, resulting in approximately 100,000 deaths each year [1]. In adults—particularly older individuals and those with chronic cardiopulmonary diseases—RSV contributes significantly to morbidity, with up to 160,000 hospitalizations and roughly 10,000 deaths annually in the United States alone [2, 3].

RSV is an enveloped, pleomorphic virus approximately 150 nm in diameter and belongs to the genus *Orthopneumovirus* within the family *Pneumoviridae*. Its genome is a linear, unsegmented, negative-sense single-stranded RNA of approximately 15.2 kb, encoding 11 proteins, including 9 structural and 2 non-structural proteins. Among the structural proteins, the viral envelope contains the fusion (F) protein, the attachment (G) protein, and the small hydrophobic (SH) protein. The F protein mediates membrane fusion between the virus and host cells, the G protein facilitates viral attachment, and the function of SH remains unclear. Both F and G proteins induce neutralizing antibodies and protective effects in animal models. Based on monoclonal antibody reactivity to F and G, RSV is classified into subtypes A and B. The SH protein, which undergoes various post-translational modifications, is thought to contribute to immune evasion during early viral replication. The matrix (M) protein, located beneath the viral envelope, links the membrane to the nucleocapsid and plays a key role in viral budding. The nucleoprotein (N), phosphoprotein (P), and RNA polymerase (L) form the ribonucleoprotein (RNP) complex, which encapsidates the viral genome and serves as the scaffold for replication and transcription. Two additional proteins, M2–1 and M2–2, regulate transcription and replication; M2–1 enhances transcription processivity, whereas M2–2 modulates the balance between replication and transcription. Near the 3′ promoter, RSV encodes two non-structural proteins, NS1 and NS2, which facilitate viral growth

by modulating the activation and response of type I, II, and III interferon (IFN) [4].

Regarding RSV management, two monoclonal antibodies (Nirsevimab, Clesroviman) are approved for preventing RSV infection in infants. However, no comparable therapeutic option exists for adults. Three new vaccines, including two protein subunit vaccines (Arexvy, Abrysvo) and one mRNA vaccine (mRESVIA), have recently been approved for older adults, with one also licensed for maternal immunization [4]. Ribavirin is currently the only medication approved by the Food and Drug Administration for the treatment of severe RSV bronchiolitis in children [5]. Therefore, there is an urgent need for effective antivirals for adults, particularly those at high risk of severe disease. Given the laborious, time-consuming, and costly nature of antiviral drug development, repurposing traditional herbal medicines and existing licensed drugs may provide a practical alternative.

Kampo medicines (KMs), such as Kakkon-to (KT), Sho-saiko-to (SST), and Saiko-keishi-to (SKT), are traditional Japanese formulations derived from traditional Chinese medicine. Approximately 150 KMs are commercially available in Japan. They are inexpensive and widely prescribed for conditions including the common cold, pulmonary and hepatic diseases, urological disorders, menopausal symptoms, and dementia. KMs primarily consist of plant-derived ingredients such as *Scutellariae Radix*, *Glycyrrhiza Radix*,

Ziziphus jujuba, *Panax ginseng*, and others. For example, SST contains *Scutellariae Radix*, *Glycyrrhiza Radix*, *Ziziphus jujuba*, *Panax ginseng*, *Bupleurum Radix*, *Pinelliae Tuber*, and *Zingiberis Rhizoma* (Table 1). During the COVID-19 pandemic, KMs—including KT, SST, Sho-saiko-to-ka-kikyo-sekko (SSTKS), SKT, and Keigai-rengyo-to (KRT)—have been successfully used clinically, with or without concomitant minocycline (MIN) [6–9]. Moreover, KT, SST, SSTKS, SKT, and MIN have been proposed as potential treatments for influenza, monkeypox, severe fever with thrombocytopenia syndrome, Crimean–Congo hemorrhagic fever, and dengue fever [10–14]. Several KM ingredients exhibit anti-RSV activity. *Scutellariae Radix*, a component of SST, SSTKS, SKT, and KRT, contains baicalin, which suppresses translation of the viral M protein and transcription of NS1 and NS2, downregulates pro-inflammatory cytokines, and induces type I IFN, thereby eliciting a strong innate antiviral response [15]. *Glycyrrhiza Radix*, a component of KT, SST, SSTKS, SKT, and KRT, inhibits RSV replication in a concentration-dependent manner in HeLa cells [16]. *Schizonepetae Spica*, a component of KRT, contains luteolin. Luteolin significantly inhibits RSV replication in a dose-dependent manner in vitro. In mice, luteolin reduced the viral titer in the lungs and alleviated the pathological damage of lung tissues. The anti-RSV effect of luteolin may be achieved by inducing the expression of miRNA-155 in host cells. The high expression of miRNA-155 can down-regulate the expression of SOCS1, which is a negative regulator of STAT1, and promote the upregulation of IFN-

stimulated gene (ISG) expression to produce an anti-RSV effect [17]. *Forsythiae Fructus*, another KRT component, contains quercetin, kaempferol, acteoside, phillyrin, and rutin. Quercetin is speculated to interact with F-protein on RSV surface that is an important region for adhesion and viral infection [18]. Moreover, quercetin effectively ameliorates RSV-induced lung inflammatory injury in the mouse model [19]. *In silico* studies suggest that quercetin binds favorably to the RSV M protein, potentially interfering with viral assembly and maturation processes [20]. Kaempferol is speculated to attenuate RSV-induced lung inflammation in mice through the JAK-STAT signaling pathway [21]. Acteoside attenuates RSV-induced lung injury by suppressing necroptosis and regulating metabolism *in vitro and in vivo* [22]. Multi-model analyses show that phillyrin exhibits potent anti-RSV activity and dose-dependently suppresses virus-induced inflammation [23]. *In silico* studies suggest that rutin may suppress inflammatory cytokines, such as IL-6 and TNF-α, by binding to TLR4/p38 MAPK, thereby ameliorating lung inflammation [24].

Among non-Kampo agents, MIN prevents RSV infection primarily by protecting host cells from RSV-induced cytopathic effects, reducing apoptosis, and enhancing innate immune responses. MIN also shows direct inhibition of RSV replication, although the exact antiviral mechanism remains unclear [25]. Similarly, micafungin, an echinocandin antifungal medication, is regarded as a leading repurposed candidate against RSV by showing strong affinity and

potent inhibition of the viral RNA polymerase using *in silico* screening and *in vitro* transcription assay [26]. From the standpoint of cost, MIN is preferable to micafungin.

Considering the potential synergistic effects of these agents, a combination of KRT and MIN may offer substantial therapeutic benefit. However, clinical trials are necessary to determine optimal dosing, treatment duration, efficacy, and tolerability before this therapy can be recommended for broader clinical use.

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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 *Puerariae Radix* 4.0 g, JP *Ziziphus jujuba* 3.0 g, JP *Ephedra Herba* 3.0 g, JP *Glycyrrhiza Radix* 2.0 g, JP *Cinnamomi Cortex* 2.0 g, JP *Paeoniae Radix* 2.0 g, JP *Zingiberis Rhizoma* 2.0 g
Sho-saiko-to (Xiao Chai Hu Tang)	JP *Bupleurum Radix* 7.0 g, JP *Pinellia Tuber* 5.0 g, JP *Scutellariae Radix* 3.0, JP *Ziziphus jujuba* 3.0 g, JP *Panax ginseng* 3.0 g, JP *Glycyrrhiza Radix* 2.0g, JP *Zingiberis Rhizoma* 1.0 g
Sho-saiko-to-ka-kikyo-sekko (Xiao Chai Hu Tang Jia Jie Geng Shi Gao)	JP *Bupleurum Radix* 7.0 g, JP *Pinellia Tuber* 5.0 g, JP *Scutellariae Radix* 3.0, JP *Ziziphus jujuba* 3.0 g, JP *Panax ginseng* 3.0 g, JP *Glycyrrhiza* Radix 2.0g,

	JP *Zingiberis Rhizoma* 1.0 g,
	JP *Gipsum Fibrosum* 10.0 g,
	JP *Platycodion Radix* 3.0 g
Saiko-keishi-to (Chai Hu Gui Zhi Tang)	JP *Bupleurum Radix* 5.0 g, JP *Pinellia Tuber* 4.0 g,
	JP *Scutellariae Radix* 2.0 g, JP *Ziziphus jujuba* 2.0 g,
	JP *Panax ginseng* 2.0 g, JP *Glycyrrhiza Radix* 2.0g,
	JP *Zingiberis Rhizoma* 1.0 g, JP *Cinnamomi Cortex* 2.0 g
	JP *Paeoniae Radix* 2.0 g
Keigai-rengyo-to (Jing Jie Lian Qiao Tang)	JP *Scutellariae Radix* 1.5 g,
	JP *Phellodendri* Cortex 1.5 g,
	JP *Coptidis Rhizoma* 1.5 g, JP *Platycodi Radix* 1.5 g,
	JP *Aurantii Fructus Immaturus* 1.5 g,
	JP *Schizonepetae* 1.5 g, JP *Bupleurum Radix* 1.5 g,
	JP *Gardeniae Fructus* 1.5 g,
	JP *Rehmanniae Radix* 1.5 g,
	JP *Paeoniae Radix* 1.5 g, JP *Cnidii Rhizome* 1.5 g,
	JP *Angelicae Acutilobase Radix* 1.5 g,

JP *Menthae Herba* 1.5 g,

JP *Angelicae Dahuricae Radix* 1.5 g,

JP *Saposhinikoviae Radix* 1.5 g,

JP *Forsythiae Fructus* 1.5 g,

JP *Glycyrrhiza Radix* 1.0 g

Table 1