Hypothesis

Treatment with Minocycline and Kampo Medicine (Kami-Kihi-To and Saiko-Keishi-To) for COVID-19 and Long COVID

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Treatment with Minocycline and Kampo Medicine (Kami-Kihi-To and Saiko-Keishi-To) for COVID-19 and Long COVID

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Abstract

Coronavirus disease 2019 (COVID-19) remains a global threat to human health because of its sporadic prevalence despite the development of COVID-19 vaccines and several drugs such as remdesivir and molnupiravir. Moreover, long COVID has become another global issue. No standard treatment has been established for long COVID. Therefore, finding quickly effective and low-priced drugs against COVID-19 and long COVID-19 and conducting clinical trials on these drugs remains crucial for global health. Drug repurposing is a well-known strategy for redeploying existing licensed drugs for newer indications, enabling the shortest possible transition from bench to bed side. Regarding existing licensed drugs for COVID-19, tetracycline has been administered since the beginning of 2020 due to its efficacy in inhibiting COVID-19 and its anti-inflammatory effects. Neuroinflammation associated with microglia in the central nervous system is considered one of the pathophysiologies of long COVID. Further, tetracycline is expected to be efficacious against long COVID because it inhibits microglial activity. Recently, minocycline has been efficacious against long COVID. Considering other existing licensed drugs for COVID-19, Kampo medicine, which is a traditional Japanese medicine, has been prescribed during the COVID-19 pandemic due to its efficacy in inhibiting severe acute respiratory syndrome corona virus 2 and its anti-inflammatory effects. Recently, Kampo medicine has been effective for long COVID. Multidrug treatment is effective because of the synergistic effects associated with the different mechanisms of action of the concerned drugs. Therefore, a combination of minocycline and Kampo medicine may be more efficacious against COVID-19 and long COVID.

Keywords: SARS-CoV-2; COVID-19; long COVID; minocycline; Kampo medicine

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Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred in late 2019 and has since become a major global health threat to humans. The development of COVID-19 vaccines brought the global pandemic closer to an end. However, COVID-19 remains sporadically prevalent due to the highly transmissible Omicron variant of SARS-CoV-2. Long COVID—also known as *post-COVID-19 condition*—is defined by the World Health Organization as a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months after the onset, with symptoms that last for at least two months and cannot be explained by an alternative diagnosis. Approximately 1 out of 5–8 people who have had COVID-19 may develop long COVID [1].

During the SARS-CoV-2 pandemic, new drugs, such as remdesivir and molnupiravir, were developed as non-vaccine treatments. They are efficacious against COVID-19 to a certain extent, but expensive. No standard treatment has been established for long COVID. Therefore, finding quickly effective and low-priced drugs against COVID-19 and long COVID-19 and conducting clinical trials on these drugs remains crucial for global health. Drug repurposing is a well-known strategy for

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redeploying existing licensed drugs for newer indications, enabling the shortest possible transition from bench to bed side for meeting therapeutic requirements.

Regarding existing licensed drugs for COVID-19, tetracycline (TC) (e.g., minocycline (MIN), and doxycycline (DOX)) has been administered since the beginning of 2020 due to its efficacy in inhibiting COVID-19 and its anti-inflammatory effects [2,3]. TCs are highly lipophilic and chelate zinc compounds on matrix metalloproteinases (MMPs). Several SARS-CoV-2 functions, including replication, are associated with the host MMP complex. Therefore, the zinc-chelating properties of TCs may help inhibit COVID-19 in humans, thereby limiting SARS-CoV-2 replication within the host [4,5]. Using an *in silico* study, Bharadwaj et al. revealed TCs to be the main protease inhibitor of SARS-CoV-2 [6]. Similarly, another *in silico* study demonstrated that TCs bind to the receptor-binding domain of the SARS-CoV-2 spike protein and prevent the SARS-CoV-2 spike protein from binding to the angiotensin-converting enzyme (ACE) II receptor [7]. Neuroinflammation associated with microglia in the central nervous system is considered one of the pathophysiologies of long COVID. Microglia mediate the overproduction of pro-inflammatory cytokines, free radicals, and damage signals, causing neurotoxic consequences. TCs possess neuroprotective and anti-inflammatory effects. Furthermore, TCs inhibit microglial activity and neuroinflammation by hindering nuclear factor kappa B signaling, cyclooxygenase 2, and MMPs [8]. Thus, TC treatment may control neuropsychiatric manifestations associated with long COVID. Regarding TC treatment for mild and moderate COVID-19, Yates et al. reported successful treatment of four patients at high-risk COVID-19 with comorbid pulmonary disease treated with DOX at 100–200 mg/day for 5–14 days [2]. Furthermore, Gironi et al. revealed that DOX and MIN improved mild COVID-19-related symptoms within 10 days [3]. Itoh et al. reported that a combination of favipiravir and MIN eliminated SARS-CoV-2 more quickly than favipiravir treatment alone while significantly reducing the interleukin (IL)-6 levels [9]. Miwa revealed that MIN treatment, administered as a 6-week regimen (100 mg × 2 on the first day, followed by 100 mg/day for 41 days), was effective in ameliorating long COVID-19 symptoms including fatigue, unrefreshing sleep and brain fog [10].

Regarding other existing licensed drugs for COVID-19, Kampo medicine (KM) (e.g., Saiko-keishi-to (SKT), Kakkon-to, and Shosaiko-to-ka-kikyosekko), a traditional Japanese medicine that is based on unique theories and therapeutic methods of traditional Chinese medicine, has been prescribed during the SARS-CoV-2 pandemic [11–14]. KM is mainly created using organic plant-based ingredients. The ingredients used to make SKT include *Ziziphus jujuba*, *Bupleurum* root, *Glycyrrhiza*, Ginseng, Ginger, etc. (Table 1). *Ziziphus jujuba* is one of the SKT components. Ursonic acid, a *Ziziphus jujuba* extract, binds to SARS-CoV-2 Nsp15, which is an endoribonuclease, and inhibits viral replication in an *in silico* study. Moreover, ursonic acid demonstrates an anti-inflammatory effect by inhibiting nitric oxide production [15]. Similarly, betulin, a *Ziziphus jujuba* extract, decreases inflammatory cytokines, particularly IFN-γ, and reduces pulmonary inflammation [15]. Further, *Bupleurum* root is one of the SKT components. Saikosaponin, a *Bupleurum* extract, demonstrates *in vitro* antiviral activity against human coronavirus 229E by dose-dependently inhibiting viral attachment to cells, blocking viral penetration into cells, and interfering with the early stages of viral replication [16]. An *in silico* study revealed that saikosaponin demonstrates a high affinity for binding to the ACE II receptor and viral main protease, which may inhibit both viral entry and replication [17]. Moreover, saikosaponin exhibit anti-inflammatory properties that inhibit pro-inflammatory cytokines, including tumor necrosis factor-α, IL-1β, IL-6 and IL-8 [18]. *Glycyrrhiza* is one of the components of SKT. Glycyrrhizin, which is a *Glycyrrhiza* extract, is expected to inhibit COVID-19 through its antiviral and anti-inflammatory effects of inhibiting the cytokine storms triggered by SARS-Cov-2 infection [19]. Ginseng is one of the SKT components. It suppresses SARS-CoV-2 replication and lowers the number of viral RNA copies. Ginseng, including ginsenosides, polysaccharides, and volatile oils, exerts immune regulatory functions to reduce the release of pro-inflammatory cytokines in animal models [20]. Peony root and Scutellaria root, which are two other components of SKT, are thought to be efficacious against SARS-CoV-2 infection by molecular modeling predictions and cell/animal experiments, respectively [21]. Regarding KM treatment for

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COVID-19 and long COVID, three cases of COVID-19 pneumonia were successfully treated with SKT in combination with other drugs [11]. The combination of MIN (100 mg, twice daily) and SKT (2.5 g, three times daily) was effective for COVID-19 in acute and subacute phases [12,13]. Ono et al. reported that a combination of SKT and Kami-kihi-to (KKT) improved the quality of life of patients with long COVID, 3 months after receiving this combination [22]. Further, KKT, which is another KM, includes ingredients, such as *Ziziphus jujuba*, *Bupleurum* root, *Glycyrrhiza*, Ginseng, and Ginger, just like SKT (Table 1). Therefore, this combination contains more of the above-mentioned ingredients than SKT only. *Poria*, which is one of the KKT components, has been used for insomnia in Asian countries for a long time [23]. Moreover, *Angelicae*, which is also one of the KKT components, is known to provide neuroprotective and anti-depression effects in animal models [24,25]. Therefore, these ingredients may help those with long COVID-related neuropsychiatric symptoms, including sleep disorders, depression, and brain fog. Multidrug treatment is effective because of the synergistic effects associated with the different mechanisms of action of the concerned drugs. Therefore, the combination of MIN, SKT, and KKT may be more efficacious against COVID-19 and long COVID.

In any case, clinical trials are warranted to better assess the optimal doses and durations, as well as the efficacy and tolerability of this combination before it can be widely used.

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