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Treatment of COVID-19-Related Olfactory Disorder Promoted by Kakkontokasenkyushin'i: A Case Series

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Olfactory disorders are one of the characteristic symptoms of the coronavirus disease of 2019 (COVID-19), which causes infection and inflammation of the upper and lower respiratory tract. To our knowledge, there are no treatments for COVID-19-related olfactory disorder. Here, we report five olfactory disorder cases in COVID-19, treated using the Japanese traditional (Kampo) medicine, kakkontokasenkyushin'i. We treated five patients with mild COVID-19 at an isolation facility using Kampo medicine, depending on their symptoms. Patients with the olfactory disorder presented with a blocked nose, nasal discharge or taste impairment. Physical examination using Kampo medicine showed similar findings, such as a red tongue with red spots and sublingual vein congestion, which presented as blood stasis and inflammation; thus, we prescribed the Kampo medicine, kakkontokasenkyushin'i. After administration, the numeric rating scale scores of the smell impairment improved within 3 days from 9 to 3 in case 1, from 10 to 0 in case 2, from 9 to 0 in case 3, from 5 to 0 in case 4, and from 9 to 0 within 5 days in case 5. Following the treatment, other common cold symptoms were also alleviated. Kakkontokasenkyushin'i can be used for treating nasal congestion, rhinitis, and inflammation in the nasal mucosa. The olfactory disorder in COVID-19 has been reportedly associated with inflammation and congestion, especially in the olfactory bulb and olfactory cleft. Kakkontokasenkyushin'i may be one of the treatment alternatives for the olfactory disorder with rhinitis in patients with COVID-19.

Keywords: blocked nose; coronavirus disease; kakkontokasenkyushin'i; Kampo medicine; olfactory disorder
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Introduction

The coronavirus disease of 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was discovered in Wuhan, Hubei, China, in November 2019. More than 75 million cases of COVID-19 have been identified worldwide, along with more than 1,660,000 deaths. In Japan, there have been over 190,000 cases of COVID-19 and over 2,600 deaths (as of December 18, 2020) (CSSEGISandData/COVID-19 2020). The Ministry of Health, Labor, and Welfare in Japan published a manual for residential care for patients with mild COVID-19 (Ministry of Health, Labour and Welfare 2020). After several patients tested positive for SARS-CoV-2 in the RNA polymerase chain reaction test (PCR test), patients in the mild stage of the disease were transferred and quarantined in isolation facilities. The management of patients varied in each prefecture or city in Japan. After admission to the facilities, mild symptoms related to COVID-19 were observed, which did not require treatment, but in some persistent cases, medical treatment was required.

The symptoms of COVID-19 vary and include fever; general fatigue; upper respiratory symptoms such as nasal

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obstruction, smell impairment, throat pain, and taste impairment; lower respiratory symptoms including cough, sputum, and shortness of breath; and gastrointestinal symptoms such as appetite loss, abdominal pain, and diarrhea (Guan et al. 2020). One of the characteristic symptoms of COVID-19 is smell and taste impairment. An altered sense of smell or taste was reported by 64.4% mildly symptomatic outpatients of COVID-19, and 34.6% of them had a blocked nose (Giacomo et al. 2020). Another survey of persistent symptoms reported that 60.4% of the patients with mild stage COVID-19 reported smell or taste impairment at baseline. At 4 weeks from symptom onset, 48.7% of the patients reported complete resolution of smell or taste impairment, 40.7% reported an improvement in the severity, and 10.6% reported no change or worsening of symptoms (Boscolo-Rizzo et al. 2020). The olfactory disorder (OD) etiology remains unclear; however, coronaviruses have been demonstrated to invade the central nervous system through the olfactory neuroepithelium and propagate from within the olfactory bulb (Dube et al. 2018). In addition, nasal epithelial cells show high expression of the angiotensin-converting enzyme 2 receptor, which is required for the entry of the SARS-CoV-2 (Sungnak et al. 2020). These reports suggest a relationship between the SARS-CoV-2 infection on the olfactory neuroepithelium and olfactory bulb and inflammation or damage in the infected tissue and neurons.

Moreover, no effective treatment or evidence for the recovery of smell impairment in COVID-19 has been elucidated (Whitcroft and Hummel 2020). Here, we report five OD cases that promptly improved following the administration of the Kampo medicine, kakkontokasenkyushin'i (KTSS), which is used for nasal congestion and rhinitis.

Case Presentation

All cases were confirmed positive in the SARS-CoV-2 PCR test conducted using nasopharyngeal swabs; the tests were performed according to the World Health Organization recommendations (World Health Organization 2020). All these cases were treated in an isolation facility at the Miyagi prefecture in Japan. The characteristics of the patients whose main symptom was smell impairment and were treated with KTSS are shown in Table 1. KTSS is a Kampo medicine composed of kakkonto (KKT) with senkyu and sin'i. Kakkonto extract contains seven crude drugs: JP (Japanese Pharmacopoeia) Pueraria root, JP Ephedra herb, JP Jujube, JP Cinnamon bark, JP Peony root, JP Glycyrrhiza, and JP Ginger (TSUMURA & CO. 2013 and Ministry of Health, Labour and Welfare 2016). The current prescription of KTSS was KTSS Extract Granules for Ethical Use made by Tsumura & Co (Fig. 1); 7.5 g of KTSS extract granules, which contain 4.0 g of a dried extract of the following mixed crude drugs: JP Pueraria Root 4.0 g, JP Jujube 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 Magnolia Flower 2.0 g, JP Cnidium Rhizome 2.0 g, and JP Ginger 1.0 g, are administered orally in three divided doses daily. TSUMURA KTSS extract granules are indicated for relief of nasal obstruction, empyema, and chronic rhinitis. The cases of this report were approved by the Ethics Committee of Tohoku University Hospital (Certificate No. 20918).

Case 1

A 36-year-old woman complained of nasal discharge and a blocked nose with a slight elevation in body temperature at 37℃ on day 1 of symptom onset. Her symptoms

Table 1. The characteristics of the patients whose main symptom was smell impairment, treated with kakkontokasenkyushin'i.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	36	18	24	44	24
Sex	female	female	female	male	male
Doctor visiting					
Days from the onset (days)	13	13	8	11	7
Temperature (℃)	36.9	36.4	36.9	36.2	36.1
SpO_2 (%)	98	98	97	98	97
Symptoms at doctor visiting					
Smell impairment	●	●	●	●	●
Taste impairment	●	●	●	●	●
Nasal discharge	●	●			●
Blocked nose	●		●	●	●
Cough					●
Sputum					●
Diarrhea					●
Fatigue					●
Duration of KTSS administration for improving smell impairment (days)	3	3	3	3	5

●, positive symptom; SpO_2, oxygen saturation; KTSS, kakkontokasenkyushin'i.

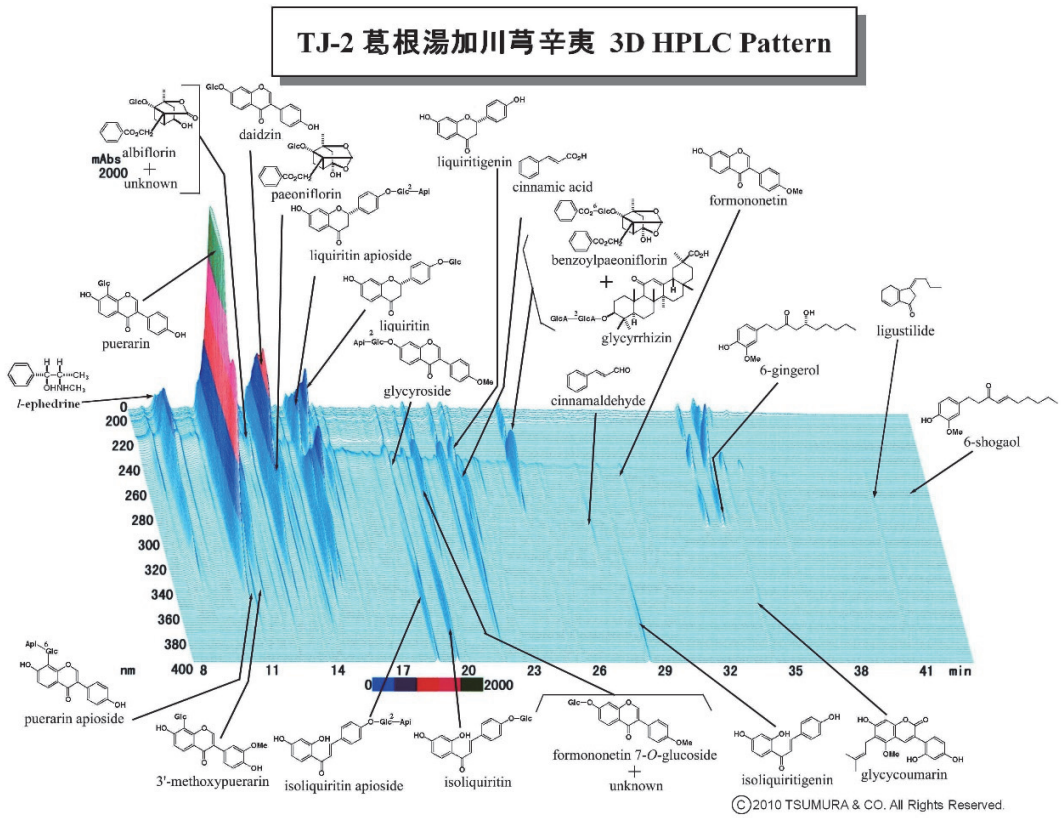

Fig. 1. Three-dimensional high-performance liquid chromatography fingerprints of Kakkontokasenkyushin'i extract granules for ethical use made by Tsumura & Co.

persisted for 5 days, and she underwent PCR testing in a drive-through outpatient clinic on day 5; she tested positive for COVID-19 on day 6. She was admitted to the isolation facility on day 8 with a complaint of smell impairment. Her blocked nose spontaneously improved by day 11; however, nasal discharge persisted, and smell impairment was severe. She consulted us for medical treatment, and we visited the facility and examined her condition on day 13. She rated her perceived smell impairment as 9/10 on the Numeric Rating Scale (NRS) at her first medical check. Her body temperature was 36.9℃ with oxygen saturation (SpO_2) of 98%, blood pressure of 109/88 mmHg, and pulse rate of 72 beats per minute. Her tongue had a slight white coating, and the sublingual vein was dilated. We diagnosed this pattern as static blood, which refers to blood stagnation according to the Kampo concept related to COVID-19, and prescribed KTSS. After administration of the Kampo medicine, smell and taste impairment improved to a score of 3/10 on the NRS within 3 days (Fig. 2). She was discharged from the isolation facility 8 days post-admission. Her taste impairment improved, and a non-recurrence of smell impairment was confirmed at the 1-month follow-up.

Case 2

An 18-year-old woman complained of nasal discharge on day 1 of symptom onset. Her symptoms persisted for over a week, and she underwent PCR testing in a drive-through outpatient clinic on day 8; she tested positive for COVID-19 on day 9. She was admitted to the isolation facility on day 10 with a complaint of smell and taste impairment. Nasal discharge spontaneously improved by day 12; however, smell and taste impairment were severe, with an NRS rating of 10/10. The smell and taste impairment continued until day 13, and she consulted for medical treatment. We visited the facility and examined her condition on day 13. The severity of her symptoms was 9/10 for smell impairment and 5/10 for taste impairment, evaluated using the NRS. Her body temperature was 36.4℃, with an SpO_2 of 98%, blood pressure of 116/74 mmHg, and pulse rate of 75 beats per minute. Her tongue was dark with a white coating, and the sublingual vein was dilated. We diagnosed this pattern as static blood related to COVID-19 and prescribed KTSS. After administration of the Kampo medicine, the smell and taste impairment improved to 0/10 on the NRS within 3 days (Fig. 3). She was discharged from the isolation facility 7 days post-admission. Her taste impairment improved, and a non-recurrence of smell impairment was confirmed at the 1-month follow-up.

Case 3

A 24-year-old woman complained of nasal discharge, blocked nose, cough, smell impairment, and fever on day 1 of symptom onset. She underwent PCR testing in a drive-through outpatient clinic on day 4 and was reported to be

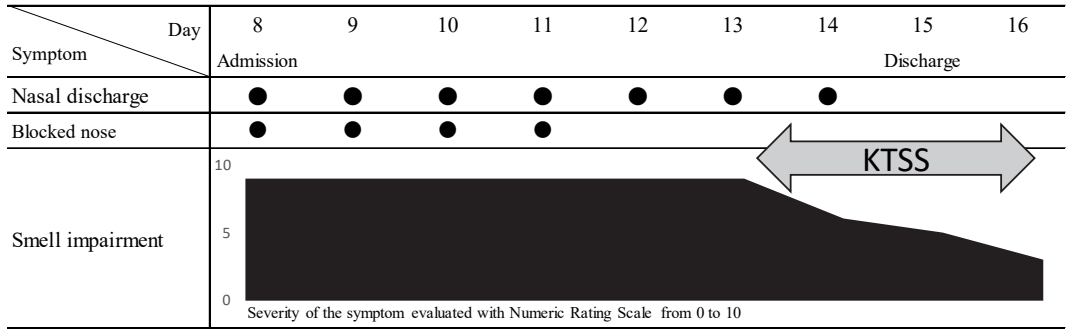

Fig. 2. Case 1 presentation and symptom course.
The severity of smell impairment was evaluated with a Numeric Rating Scale from 0 to 10. The presence of the other symptoms is indicated by the black circles. KTSS, kakkontokasenkyushin'i.

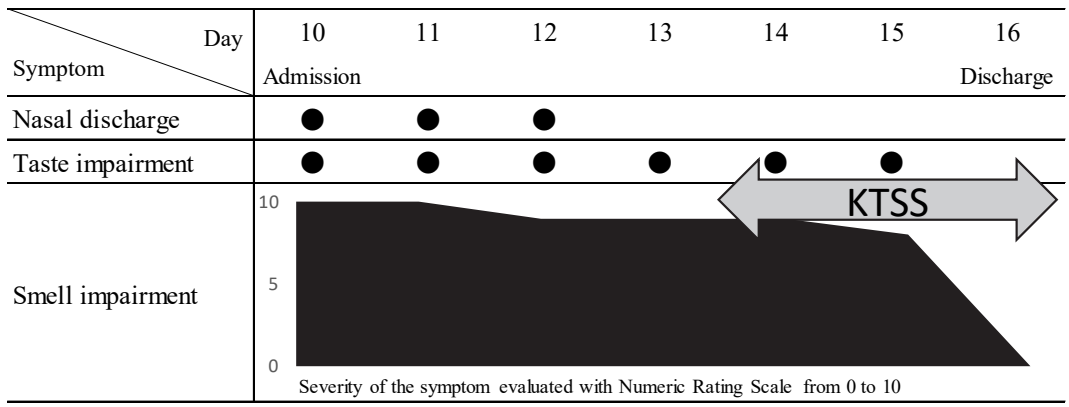

Fig. 3. Case 2 presentation and symptom course.
The severity of smell impairment was evaluated with a Numeric Rating Scale from 0 to 10. The presence of the other symptoms is indicated by the black circles. KTSS, kakkontokasenkyushin'i.

positive for COVID-19 on day 5. She was admitted to the isolation facility on day 6 with a complaint of cough, nasal discharge, blocked nose, smell impairment, and taste impairment. Cough spontaneously improved by day 7; however, other symptoms persisted, and the patient requested medical treatment. We visited the facility and examined her condition on day 8. The severity ratings of her complaints, as evaluated on the NRS, were as follows: 3/10 for blocked nose, 9/10 for smell impairment, and 7/10 for taste impairment. Her body temperature was 36.9℃, with an SpO_2 of 97%, blood pressure of 108/79 mmHg, and pulse rate of 88 beats per minute. Her tongue was red with dilation of the sublingual vein. We diagnosed this pattern as static blood related to COVID-19 and then prescribed KTSS. After the administration of Kampo medicine, smell and taste impairment improved to 3/10 on NRS within 3 days (Fig. 4). She was discharged from the isolation facility 6 days post-admission. The taste impairment improved, and a non-recurrence of smell impairment was confirmed at the 1-month follow-up.

Case 4

A 44-year-old man complained of slight fever at 37.5℃ with general fatigue on day 1 of symptom onset. His symptoms worsened on day 2 with a sore throat, nasal obstruction, smell impairment, and cough. He underwent a PCR test in a drive-through outpatient clinic on day 3 and tested positive on day 4. He was admitted to the isolation facility on day 5 with a complaint of blocked nose, smell impairment, cough, sputum, and diarrhea. In particular, nasal obstruction and smell impairment were severe, with an NRS score of 10/10. Blocked nose and smell impairment persisted on day 10, and he yearned for medical treatment. We visited the facility and examined his condition on day 11. The severity of his complaints was evaluated using the NRS, and it was rated as 7/10 for blocked nose, 5/10 for smell impairment, and 5/10 for taste impairment. His body temperature was 36.2℃, with an SpO_2 of 98%, blood pressure of 135/98 mmHg, and pulse rate of 88 beats per minute. His tongue was a dark red color with a yellow coating, and the sublingual vein was dilated. We diagnosed this pattern as static blood related to COVID-19 and prescribed KTSS. After administration of the Kampo medicine, nasal obstruction and smell impairment improved to 0/10 on the NRS within 3 days (Fig. 5). He was discharged on day 13 post-admission. His taste impairment improved, and the

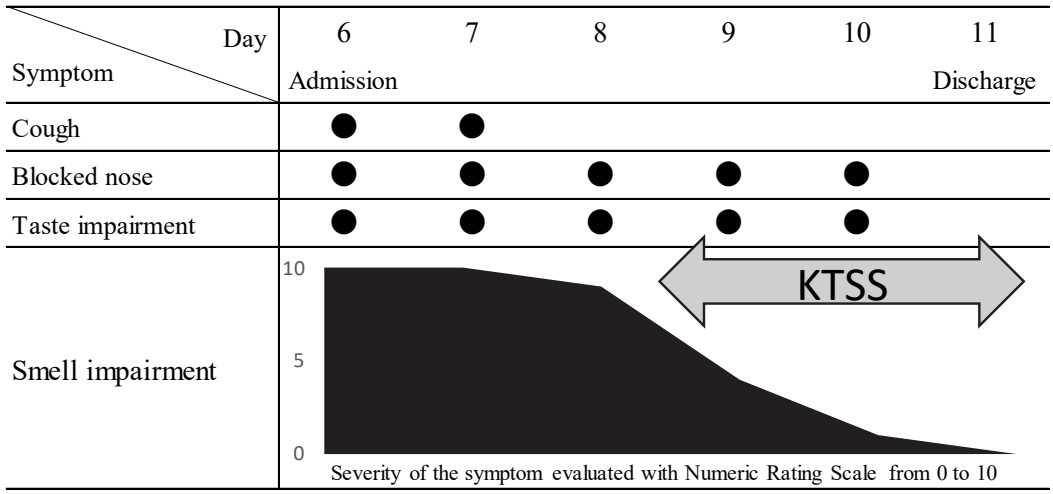

Fig. 4. Case 3 presentation and symptom course.
The severity of the symptom of smell impairment was evaluated with a Numeric Rating Scale from 0 to 10. The presence of the other symptoms is indicated by the black circles. KTSS, kakkontokasenkyushin'i.

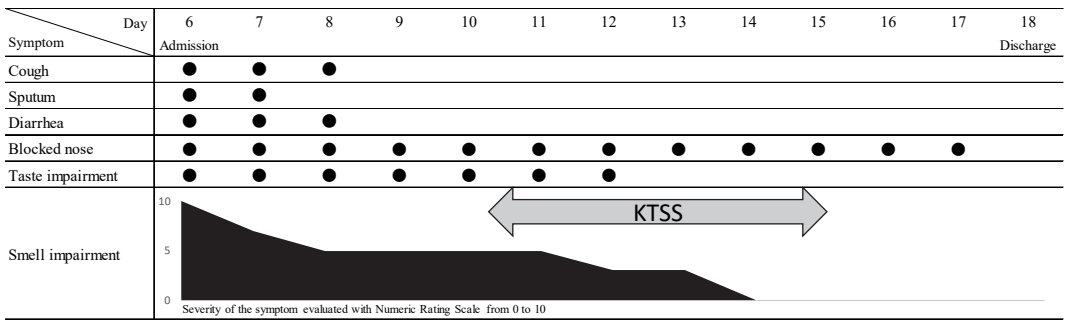

Fig. 5. Case 4 presentation and symptom course.
The severity of smell impairment was evaluated with a Numeric Rating Scale from 0 to 10. The presence of the other symptoms is indicated by the black circles. KTSS, kakkontokasenkyushin'i.

non-recurrence of smell impairment was confirmed at the 1-month follow-up.

Case 5

A 24-year-old man came in close contact with patients with COVID-19. He underwent PCR testing in a drive-through outpatient clinic on day 4 and was reported to be positive for COVID-19 on day 5. He was admitted to the isolation facility on day 6 with high fever, cough, sputum, diarrhea, fatigue, blocked nose, nasal discharge, and smell and taste impairment. He was treated on day 7 under facility visit care. The severity of his complaints was rated on the NRS as follows: 5/10 for blocked nose, 5/10 for nasal discharge, 10/10 for smell impairment, and 9/10 for taste impairment. His body temperature was 36.1℃, with an SpO_2 of 97% and pulse rate of 80 beats per minute. His tongue had a yellow coating, tooth marks, and the sublingual vein was dilated. We diagnosed this pattern as a heat damp with static blood related to COVID-19 and then prescribed KTSS and makyokansekito. After the administration of Kampo medicine, smell impairment, blocked nose, and nasal discharge improved, as revealed by 0/10 points on the NRS within 5 days (Fig. 6). The cough persisted on day 11, and we changed the prescription to makyokansekito and saireito. All symptoms were alleviated in 2 days since the new prescription. No recurrence of any symptoms was confirmed at the 1-month follow-up.

Discussion

We report a case series on the OD related to COVID-19 that possibly improved with KTSS treatment. Early recovery with no recurrence or relapse from the OD related to COVID-19 may be promoted by KTSS. KTSS, including its components for treating inflammation and congestion in the nasal mucosa, is used for the treatment of nasal congestion related to common cold or rhinitis. This Kampo medicine is permitted in the National Health Insurance system of Japan and listed in the JP 17th Edition (Ministry of Health, Labour and Welfare 2016).

Causes of OD are varied; secondary to sinonasal dis-

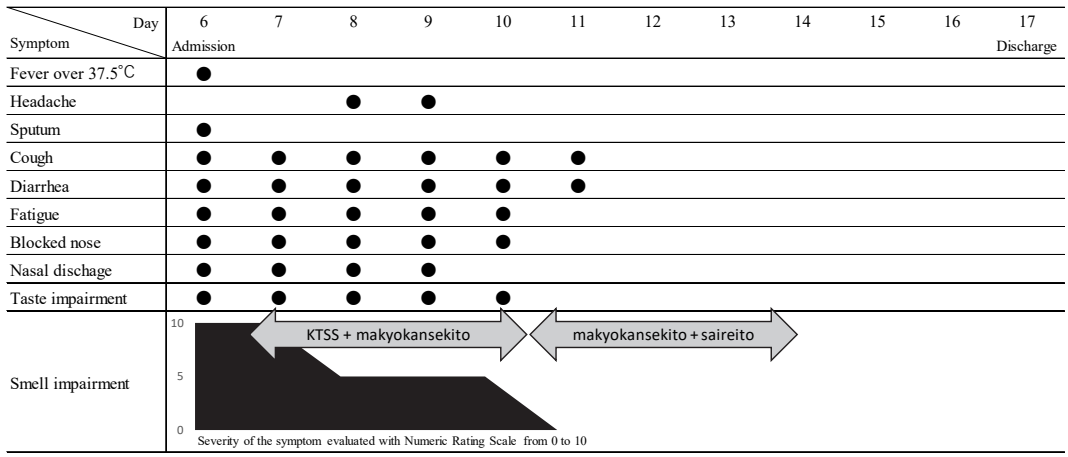

Fig. 6. Case 5 presentation and symptom course.
The severity of smell impairment was evaluated with a Numeric Rating Scale from 0 to 10. The presence of the other symptoms is indicated by the black circles. KTSS, kakkontokasenkyushin'i.

ease, postinfectious, posttraumatic, associated with neurological disease, associated with exposure to drugs/toxins, congenital, associated with aging, iatrogenic damage, tumors, multiple systemic co-morbidities, and idiopathic (Hummel et al. 2017). The most common causes of postinfectious OD are viruses, including those causing the common cold, influenza, and human immunodeficiency virus (Suzuki et al. 2007; Philpott and DeVere 2013). The pathophysiology is thought to involve either damage to the olfactory neuroepithelium or central olfactory processing pathways (Youngentob et al. 2001; Baker and Genter 2003) and neuroepithelial remodeling, reducing olfactory sensory neurons and receptors (Jafek et al. 2002).

We have no data of patients with OD without treatment. Still, the OD of COVID-19 has a sudden onset in the majority of cases and is usually a transient entity, with a median time to recovery ranging between 1 and 3 weeks (Lee et al. 2020). No significant association with sinonasal symptoms has been identified, suggesting that the pathogenesis of COVID-19 anosmia might differ from that of obstructive olfactory dysfunction seen in other upper respiratory tract viral infections (Cooper et al. 2020; Han et al. 2020). The pathogenesis of COVID-19 anosmia has not been fully defined; however, plausible mechanisms include olfactory cleft inflammation/obstruction and/or olfactory bulb damage (Cooper et al. 2020; Han et al. 2020). Nasal epithelial cells show high expression of the angiotensin-converting enzyme 2 receptor, which is required for the entry of the SARS-CoV-2 (Sungnak et al. 2020). The disruption of cells in the olfactory neuroepithelium may result in inflammatory changes that impair olfactory receptor neuron function, causing olfactory receptor neuron damage and/or impairing subsequent neurogenesis. Such changes may result in short-term or long-term OD. Using animal models, the intracranial entry of SARS-CoV via the olfactory bulb has been demonstrated (Netland et al. 2008). Patients with COVID-19 anosmia have higher olfactory cleft widths and volumes, as evaluated using computed tomography (CT) and magnetic resonance imaging. The increased signal intensity of the olfactory cleft mucosa was also detected in COVID-19 anosmia, suggestive of inflammatory changes (Altundag et al. 2020). Olfactory bulb degeneration and olfactory cleft opacification were observed on CT in persistent COVID-19 anosmia cases. Mucosal edema with subsequent narrowing of the olfactory cleft may cause inflammatory changes in the olfactory clefts due to viral invasion (Kandemirli et al. 2021). According to these possible etiologies and imaging findings in OD related to COVID-19, the treatment strategy may include antiviral and anti-inflammatory actions, improvement of mucosal edema, and relieving neural damage.

Treatments for postinfectious OD may potentially be helpful for COVID-19. Olfactory training involves repeat and deliberate sniffing of a set of odorants. Oral and intranasal corticosteroids against inflammation, intranasal sodium citrate, intranasal vitamin A, and systemic omega-3 administration were used for postinfectious OD (Whitcroft and Hummel 2020). Regarding the treatment for OD related to COVID-19, corticosteroids are not currently recommended for postinfectious ODs considering the possible side effects; there is a lack of evidence on the effectiveness of these therapies in patients with OD related to COVID-19 (Sungnak et al. 2020). Lechien et al. (2020) reported the treatment for OD-related COVID-19 performed in a clinical setting. Nasal saline irrigations, nasal corticosteroids, oral corticosteroids, and others (e.g., vitamins, non-corticosteroid decongestants, and trace elements) were used for OD (Lechien et al. 2020).

Kurokawa et al. (2002) reported that KKT increased the levels of interleukin (IL)-12, which promoted the differentiation of naïve T cells into Th1 cells in the bronchoalveolar lavage fluid in the early phase of a viral infection. Geng et al. (2019) reported that KKT reduced the expression of IL-1α, IL-6, and tumor necrosis factor (TNF)-α,

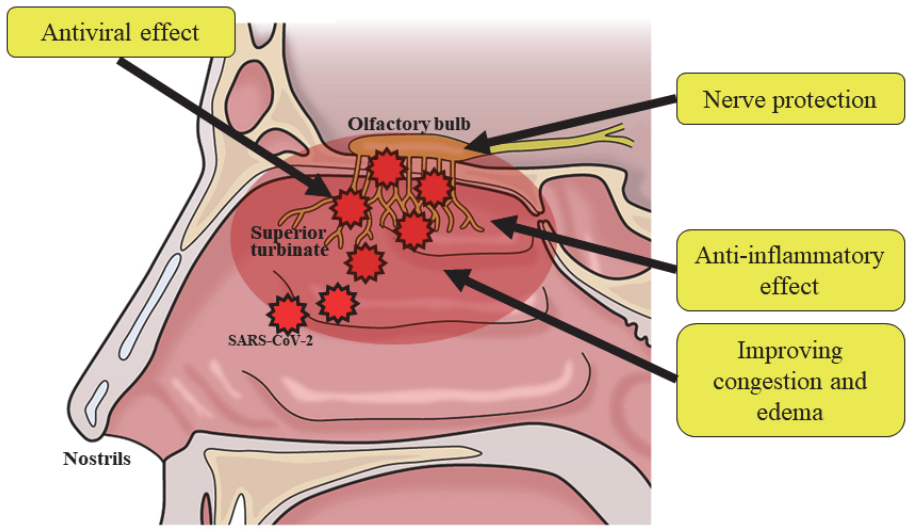

Fig. 7. The possible mechanisms of KTSS for the treatment of olfactory disorder in COVID-19.
The SARS-CoV-2 infects the superior turbinate and then invades the olfactory bulb and nerve, causing inflammation in the infected area. KTSS has antiviral effects, anti-inflammatory effects, provides nerve protection, and improves congestion and edema in the local infected area.
KTSS, kakkontokasenkyushin'i.

which are pro-inflammatory cytokines whose overexpression caused lung injury. Moreover, KKT treatment improved the Th1/Th2 imbalance, which was mediated by a decrease in interferon-gamma (IFN-γ) and IL-4 levels (Geng et al. 2019). Kitamura et al. (2014) reported that KKT treatment suppressed lipopolysaccharide (LPS)-induced prostaglandin E2 production by decreasing cyclooxygenase-1 activity. This activity is mediated by the suppression of extracellular signal-regulated kinase phosphorylation, which leads to the production of cytoplasmic phospholipase A2 (Kitamura et al. 2014). Choi et al. (2018) reported that ligustilide, which is one of the components of senkyu, suppresses vasculitis and the expression of cell adhesion molecules and TNF-α. Venkatesan et al. (2018) reported that falcarindol, which is one of the components of senkyu, inhibits LPS-induced inflammation via attenuating mitogen-activated protein kinases, janus kinase-signal transducers, and activators of transcription signaling pathways in murine macrophage RAW 264.7 cells. Tran et al. (2018) also reported that components of senkyu suppressed inflammatory reactions in a RAW 264.7 cell experiment. Ramalingam and Yong-Ki (2010) reported that senkyu suppressed the production of free radicals. Ma et al. (2020) reported that lignans from sin'i have neuroprotective effects. Oshima et al. (2020) reported that flower parts of sin'i have inhibitory activities against IL-2 production. Jung et al. (1998) reported that tiliroside from the flower buds of sin'i has an anti-complement activity. Tsuruga et al. (1991) reported that constituents of sin'i inhibit the release of histamine from rat mast cells. Kimura et al. (1985) reported that neolignans from sin'i have an anti-inflammatory effect. KTSS has an alkylperoxyl radical scavenging activity (Hirayama et al. 2018). It may contribute to the suppression of cell and tissue damage (Clinical significance of redox effects of Kampo formulae, a traditional Japanese herbal medicine: comprehensive estimation of multiple antioxidative activities 2018). The possible mechanism of KTSS for the treatment of OD in COVID-19 is shown in Fig. 7. The SARS-CoV-2 infects the superior turbinate and then invades the olfactory bulb and nerve, causing inflammation in the infected area. Taken together, these prior reports suggest that KTSS has antiviral and anti-inflammatory effects, improves mucosal edema and tissue of the olfactory bulb and olfactory cleft, and protects against neural damage. Thus, this medicine has the potential of contributing to recovery from OD. The other candidates for COVID-19-related OD may be Kampo medicines such as shoseiryuto, keigairengyoto, shin'iseihaito, kakkonto, and shigyakusan. They were permitted in JP for nasal symptoms such as rhinitis, allergic rhinitis, chronic rhinitis, empyema, nasal obstruction, coryza, and nasal catarrh.

As an integrative therapy, Kampo medicine is recommended for many diseases, conditions, and symptoms in several clinical practice guidelines in Japan (Kojima et al. 2016; Takayama and Iwasaki 2017; Takayama et al. 2018). The World Health Organization published the eleventh revision of the International Statistical Classification of Diseases and Related Health Problems in 2019, and traditional medicine was featured for the first time as a traditional medicine module (Lam et al. 2019). Traditional medicine, including Japanese Kampo medicine, has been used in combination with western medicine for many intractable diseases and conditions (Kikuchi et al. 2017; Takayama et al. 2017, 2019; Ohsawa et al. 2021; Shimizu et al. 2021; Suzuki et al. 2021), and it may be widely

applied as a new approach for COVID-19. A recent report suggested Kampo medicines, kakkonto and shosaikotokaki-kyosekko, can be used for viral infections due to their anti-viral, immunomodulatory, and anti-inflammatory effects (Arita et al. 2020). Irie et al. (2020) also reported the successful treatment of three mild stage COVID-19 cases with this combination of Kampo medicine.

The present study's limitation is that it presents a case series with no control cases. Further controlled studies, including control and blood sampling data, are warranted for collecting more evidence regarding the efficacy of Kampo medicine in the treatment of COVID-19. The Japan Society of Oriental Medicine has been leading the research for COVID-19, called Integrative Management in Japan for Epidemic Disease (IMJEDI Study-Observation) (Takayama et al. 2020a, b, c; Namiki et al. 2021). These studies have been based on prior clinical and pharmacological studies on Kampo medicine (Arita et al. 2020; Irie et al. 2020; Takayama et al. 2020a, b, c; Namiki et al. 2021) and will explore the role of Kampo medicine, including KTSS, in treating COVID-19.

We have reported five cases of OD in COVID-19 treated with KTSS. KTSS can be used for treating nasal congestion, rhinitis, and inflammation in the nasal mucosa. OD in COVID-19 has been reported to be associated with inflammation and congestion, especially in the olfactory bulb and olfactory cleft. Thus, KTSS may be considered as a treatment alternative for the OD related to COVID-19.

Acknowledgments

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Conflict of Interest

S.T., A.K., M.O. and T.I. belong to the Department of Kampo and Integrative Medicine at Tohoku University School of Medicine. The department received a grant from Tsumura, a Japanese manufacturer of Kampo medicine; however, the grant was used as per Tohoku University rules. Potential conflicts of interests were addressed by the Tohoku University Benefit Reciprocity Committee and were managed appropriately.

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