Effectiveness of Kampo Medicines Against Intractable Stomatitis: A Mini-Review

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Abstract

Intractable stomatitis is a chronic inflammatory disease of oral mucosa, with unclear etiopathogenesis. Kampo Medicines (KMs), i.e., Japanese herbal medicines, effectively treat stomatitis. The precise effects of KMs on intractable stomatitis are not established. We present the details of several patients with intractable stomatitis who were well-treated with KMs (i.e., Inchinkoto, Orento, Goreisan, and Byakkokaninjinto). We also review the literature on the link between intractable stomatitis and KMs. KM-related anti-inflammatory and antioxidant activity may suppress intractable stomatitis. KMs may also facilitate wound healing through increased saliva secretion. KMs may therefore be useful for the treatment of intractable stomatitis.

Keywords: Anti-Inflammatory Activity, Antioxidant Activity, Intractable Stomatitis, Kampo Medicines, Saliva Secretion

1. Introduction

Intractable stomatitis is not strictly defined, but it is generally considered a chronic inflammatory disease of oral mucosa. Recurrent Aphthous Stomatitis (RAS) is a type of intractable stomatitis characterized by round or ovoid ulcers with erythematosus haloes and a gray-white pseudomembrane[1–3]. Another type of intractable stomatitis, i.e., Oral Lichen Planus (OLP), is morphologically classified into reticular, papular, plaque, erythematos, atrophic, erosive, and vesiculo-bullous forms[4–7]. Although, several potential factors of intractable stomatitis types such as RAS and OLP have been considered, the etiopathogenesis of intractable stomatitis remains unknown.

Numerous topical treatments have been proposed as curative medicines for intractable stomatitis, but the treatment for these diseases remains nonspecific. Kampo Medicines (KMs), i.e., Japanese herbal medicines have been shown to be effective for treating stomatitis[8]. In particular, the KMs Inchinkoto, Hangeshashinton, and Orento are indicated for the relief of stomatitis in Japanese health insurance system. The KMs Goreisan and Byakkokaninjinto are thought to be helpful in the treatment of xerostomia. We have successfully treated several patient’s with intractable stomatitis with various KMs, as detailed in Table 1. However, the effects of KMs on intractable stomatitis have never been specified. We thus reviewed the literature on the link between intractable stomatitis and the KMs.

2. Etiopathogenesis of Intractable Stomatitis and the Action Mechanism of Kampo Medicines

Although the etiopathogenesis of intractable stomatitis has not been established, some type of immune-mediated pathogenesis and pathological roles of Reactive Oxygen Species (ROS) have been considered[4-6,9,10]. It is not known how KMs act against intractable stomatitis, but many KMs have anti-inflammatory and antioxidant activity that may be involved in this action[8,10,11]. Inchinkoto contains the following herbal extracts: Artemisia capillaris flower,
gardenia fruit, and rhubarb. Artemisia capillaris flower and gardenia fruit have anti-inflammatory activity [12-14], and Artemisia capillaris flower reduces the expression of the proinflammatory cytokine tumor necrosis factor-alpha (TNF-α) [14]. TNF-α plays important roles in the development of intractable stomatitis such as RAS and OLP [15,16]. Artemisia capillaris flower, gardenia fruit, and rhubarb have antioxidant activity [14,17-21]. In particular, gardenia fruit induces the expression of NF-E2 related factor 2 (Nrf2) mRNA, which is followed by an upregulation of antioxidant response element (ARE)-mediated genes such as heme oxygenase-1 (HO-1) [22-25]. Hangeshashinto contains the following herbal extracts: pinellia tuber, coptis rhizome, processed ginger, glycyrrhiza, jujube, ginseng, and scutellaria root. Orento contains the following herbal extracts: pinellia tuber, coptis rhizome, processed ginger, glycyrrhiza, jujube, ginseng, and cinnamon bark. Coptis rhizome, glycyrrhiza, scutellaria root, and cinnamon bark have anti-inflammatory activity [10,13,26,27]. More specifically, cinnamon bark blocks the activation of the Mitogen-Activated Protein Kinases (MAPKs) known as Extracellular-Signal-Regulated Kinases (ERKs), cJun NH2-terminal kinases (JNKs), and p38 MAPKs [28], and the use of cinnamon bark resulted in a reduction of TNF-α expression [28]. Glycyrhiza, ginseng, and cinnamon bark have antioxidant potential to scavenge hydroxyl radicals [27,29]. Goreisan is composed of five medicinal plants: Alisma rhizome, Atractylodes lancea rhizome, Polyoporus sclerotium, Poria sclerotium, and cinnamon bark. As noted above, cinnamon bark has anti-inflammatory activity [26,27], antioxidant potential [27], and it reduces TNF-α expression [28]. Byakkokaninjinto is composed of the following medicinal plants: gyspum, anemarrhena rhizome, glycyrhiza, ginseng, and brown rice. Byakkokaninjinto increases the expression of the membrane protein aquaporin (AQP) 3 [30], which regulates water balance [31]. AQP3 promotes keratinocyte proliferation and differentiation [32], and facilitates wound healing [32,33]. Byakkokaninjinto and gosirens enhance salivary secretion [34,35]. In fact, Byakkokaninjinto activates muscanrinic acetylcholine receptor M3 [34], and it increases the expression of AQP 5 [34], which regulates salivary secretion. In our patients treated with Byakkokaninjinto, salivary flow increased. Goreisan and Byakkokaninjinto may secondarily facilitate wound healing through increased saliva secretion. We have thus observed curative effects of the KMs on intractable stomatitis that are consistent with the reports cited above. Although our patients had been struggling with intractable stomatitis for years, no exacerbation of their intractable stomatitis has occurred since their treatment with KMs. Moreover, the effects of KMs on intractable stomatitis may be not only curative but also preventive.

### 3. Conclusion

The etiopathogenesis of intractable stomatitis is unclear, but it is possible that the anti-inflammatory and antioxidant activities of KMs suppress intractable stomatitis. KMs may facilitate wound healing through increased saliva secretion. In any case, there are many reports of the effectiveness for the treatment of intractable stomatitis.

### 4. Conflicts of Interest

The authors have no conflict of interests to declare regarding this study or the publication of this paper.

### 5. Acknowledgements

This work was supported by JSPS KAKENHI, Grant Number 16K11888.
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How to cite this article: Momota Y., Takano H. & Azuma M. Effectiveness of Kampo Medicines Against Intractable Stomatitis: A Mini-Review. J. Med. Dent. Sci. 2019; 8(2): 1724-1727.