

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 erythematous 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, erythematous, 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, Hangeshashinto, 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 patients 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,

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Table 1. The patient's clinical characteristics

Case	Age	Sex	Site	Diagnosis	Kampo medicines
1	79	Female	Upper and lower gingiva	OLP	Inchinkoto (2.5 g/day) + Goreisan (7.5 g/day)
2	71	Female	Tongue	RAS	Inchinkoto (2.5-7.5 g/day) + Byakkokaninjinto (9.0 g/day)
3	76	Female	Lower lip	RAS	Inchinkoto (7.5 g/day)
4	68	Female	Lower gingiva	OLP	Orento (5.0-7.5 g/day) + Goreisan (5.0-7.5 g/day)
5	65	Male	Tongue	Ulcer	Inchinkoto (2.5-7.5 g/day) + Goreisan (2.5 g/day)
6	72	Female	Lower gingiva	RAS	Inchinkoto (7.5 g/day)
7	18	Female	Lower lip	RAS	Inchinkoto (2.5-7.5 g/day)

OLP, oral lichen planus; RAS, recurrent aphthous stomatitis.

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- α (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]. Glycyrrhiza, 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, *Polyporus 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: gypsum, *Anemarrhena* rhizome, glycyrrhiza, 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 goreisan enhances salivary secretion^[34,35]. In fact, Byakkokaninjinto activates muscarinic 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.

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