Bambusae Caulis in Taeniam Applicable for Medical Indications Associated with Inflammation

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Jukyeo (竹茹; Bambusae Caulis in Taeniam: BCT) is an herbal medicine made from the inner part of the bamboo stem of *Phyllostachys nigra* Munro var. *henonis* Stapf ex Rendle or *Phyllostachys bambusoides* Siebold et Zuccarini. Although medical literature published in China and Korea decades ago introduced BCT as a remedy for reducing vomiting, fever, and hematemesis, decoctions containing BCT as a main herb (君藥) in Korea have been approved only for treating neurologic symptoms. Here, we discuss the anti-inflammatory function of BCT. Combined with the clinical usage of a BCT-containing decoction in treating inflammatory diseases in Japan, we raise the possibility of repurposing the BCT-containing decoctions for treating inflammatory diseases. The anti-inflammatory activity of BCT was mainly assessed by using RAW 264.7 cells. The regulation of NF-κB, Nrf2 and A20 activities was determined by western blot and quantitative RT-PCR. The list of decoctions containing BCT currently approved in Korea was obtained from the Korean Ministry of Food and Drug Safety (KFDA). BCT suppressed the activity of pro-inflammatory factor NF-κB elicited by LPS, activated an anti-inflammatory factor Nrf2, and induced A20 that is known to block several inflammatory pathways simultaneously, suggesting that BCT can suppress inflammation via at least 3 different pathways. KFDA approved 11 decoctions containing BCT as a major herb, including Gamiondam-tang (加味溫膽湯; GOT), for treating neurologic disorders. Interestingly, Jukyeoondam-tang (竹茹溫膽湯; JOT), whose composition is almost identical to GOT except for one herb, has been used to treat inflammatory pulmonary disorders including Covid-19 pulmonary infection in Japan Given the anti-inflammatory function of BCT evidenced by medical literature and experimental results and the clinical usage of JOT in treating inflammatory pulmonary disorders, we suggest a repurposing and extension of the BCT-containing decoctions approved in Korea to treating inflammatory diseases.

keywords : Jukyeo(Bambusae Caulis in Taeniam), Decoctions, Repurposing, Medical indications

Introduction

Jukyeo (竹茹; Bambusae Caulis in Taeniam: BCT) is an herbal medicine made mostly from *Phyllostachys nigra* Munro var. *henonis* Stapf ex Rendle or *Phyllostachys bambusoides* Siebold et Zuccarini[1)]. These two bamboo plants belong to the family Gramineae and inhabit mainly China, Japan, and Korea[2)]. BCT is prepared by peeling off the outer layer of the bamboo stems; the resultant inner part of the stems is sliced and dried in a shaded place[3)]. The first description of BCT can be traced back to a Chinese medical book by Do Hong Kyung (陶弘景, AC 456-536) in the Yang Dynasty of China. According to the medical book, BCT was used to treat symptoms such as vomiting, shivering, fever, spewing blood (hematemesis), and vaginal bleeding[4)]. Dongeuibogam (東醫寶鑑) written by Heo Jun (許浚) also denoted that the bamboo peeled off the blue skin is useful to treat vomiting, hiccup, hematemesis, phlegm, and vaginal bleeding[5)]. Given that inflammation results in extravascular exudate due to increased cellular infiltration and blood flow, along with fever and goblet cell activation[6)], the clinical indications (適應症) or symptoms assigned to BCT can be interpreted as an anti-inflammatory activity. Here, we discuss the anti-inflammatory activity of BCT by providing the evidence of possible pathways by which BCT suppresses inflammation. In addition, comparing the constituent herbs in BCT-containing decoctions used in Korea and Japan, we raise the possibility of repurposing or expanding the indications of BCT-containing decoctions to treating inflammatory diseases.

Main Body

1. Experimental evidence for BCT to ameliorate inflammatory

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diseases

According to modern herbology, BCT can be prescribed to treat phlegm discharge caused by upper respiratory infection or pneumonia and to ease chronic gastritis or morning sickness[7]. These effects are accordant with the herbal characteristics of BCT, in that BCT has a sweet, yet chilling characteristic and its therapeutic effects converge mainly on the lung and stomach. However, limited studies are available that support the regulatory role of BCT in inflammatory diseases.

A recent study showed that BCT can be used to treat chronic obstructive pulmonary disease (COPD), a chronic inflammatory lung disease. In a cigarette-smoke-induced COPD mouse model, BCT reduced the expression of the prototypic pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, and the infiltration of inflammatory cells, such as macrophages and neutrophils, in mouse lungs[8], suggesting that BCT has an anti-inflammatory function. Consistent with this result, p-coumaric acid, a primary chemical found in BCT, plays a role in suppressing inflammation in a similar mouse model[9]. BCT was also reported to reduce the inflammatory symptoms associated with rheumatoid arthritis (RA)[10], the patients of which suffer from the degradation of proteins constituting cartilage and bone by various matrix metalloproteases (MMPs)[11]. MMP-3 is one of the metalloproteases involved in RA[12], whose production can be suppressed by BCT[13]. Similarly, Bambusae caulis in Liquamen (BCL), a liquid extract of bamboo stems, suppressed inflammation in a 2,4-dinitrochlorobenzene (DNCB)-induced atopic dermatitis (AD) mouse model[14]. In the study, BCL was shown to decrease inflammatory cell infiltration into a skin lesion and the production of TNF-α and IFN-γ that exacerbate AD. It was reported that BCT can relieve hypertension and cardiovascular disease[3]. Given that inflammation is one of the underlying causes of hypertension and cardiovascular diseases[15], the relieving effect of BCT could be due to inflammation suppressed by BCT. Together, these results suggest that the bamboo stem has anti-inflammatory activity, ameliorating various inflammatory diseases. As yet, however, no clinical studies with patients of COPD, RA, or AD are reported to consolidate these results.

2. Three possible anti-inflammatory mechanisms exerted by BCT

Although the results indicate that BCT has an anti-inflammatory function, it is less understood how BCT suppresses inflammation. One of the possible mechanisms for BCT to suppress inflammation is via suppressing NF-κB activity. In COPD mice, BCT decreased the production of IL-1β, IL-6, and TNF-α[8]. Since the expression of these cytokines is largely governed by NF-κB[16,17], it was examined whether BCT inhibits NF-κB activity. Indeed, the study revealed that BCT suppresses NF-κB activity[8], for which p-coumaric acid, a major chemical found in BCT, plays a key role[9]. Concordant with these findings, we also found that BCT suppressed NF-κB activity. In our experiment, RAW 264.7 cells were treated with two different amounts of BCT (10 ng/ml or 50 ng/ml) for 16 hours and then with TLR-4 specific LPS to activate NF-κB in a TLR4-specific manner. We found that BCT suppressed the nuclear localization of NF-κB, suggesting BCT suppressing NF-κB. In similar experiments, where RAW 264.7 cells were treated with BCT and then with LPS (100 ng/ml) for 4 hours to induce NF-κB-dependent genes, BCT suppressed the TNF-α and IL-1β mRNA expression (data unpublished). Together, these results suggest that one of the anti-inflammatory pathways is via suppressing NF-κB activity.

The second possible mechanism is via activating the nuclear erythroid-2-related factor 2 (Nrf2). BCT was reported to increase heme oxygenase-1 (HO-1) expression by activating Nrf2 in RAW 264.7 cells[18]. BCT also activates Nrf2 in microglial BV2 and hippocampal HT22 cells, protecting these cells from LPS-induced neuro-inflammation and glutamate-induced cytotoxicity, respectively[19]. As a transcription factor, Nrf2 regulates the expression of cytoprotective and detoxifying genes, including glutamate-cysteine ligase catalytic subunit (GCLC), NAD(P)H:quinine oxidoreductase-1 (NQO1), and HO-1[20]. Along with the anti-oxidative , Nrf2 suppresses inflammation because the absence of Nrf2 exacerbates inflammatory diseases, including acute lung injury (ALI)[21], chronic obstructive pulmonary disease (COPD)[22], asthma[23], and sepsis[24]. Given the anti-inflammatory role of Nrf2, activating Nrf2 is one of the pathways that BCT suppresses inflammation. In support of this, our studies revealed that BCT activates Nrf2 (data unpublished). If RAW 264.7 cells were treated with two different amounts of BCT (10 ng/ml or 50 ng/ml) for 16 hours, Nrf2 is translocated to the nucleus, indicative of activated Nrf2. In similar experiments, BCT induced the expression of HO-1, GCLC, and NQO-1, whose expression is regulated by Nrf2. Along with others, these results further support that BCT suppresses inflammation via activating Nrf2.

The third possible pathway is via inducing A20 or tumor necrosis factor-induced protein 3 (TNFAIP3), an

anti-inflammatory adaptor molecule that suppresses NF-κB activity[17]. An inflammatory environment triggers the expression of A20, which blocks the IL-1β receptor- or TLR4-mediated signaling, decreasing the expression of pro-inflammatory cytokines and consequently inhibiting inflammation[25]. Given the anti-inflammatory role of A20, we examined whether BCT induces A20 expression. RAW 264.7 cells were treated with increasing amounts of BCT for 16 h. Western blot analysis of cytosolic proteins showed that BCT induced the expression of A20 (data unpublished). While further studies are necessary to consolidate BCT activating A20, these results suggest that BCT can suppress inflammation in at least three different ways: suppressing NF-κB, activating Nrf2, and inducing A20.

3. Repurposing the indications (適應症) treated by the BCT-containing decoctions

Given that BCT has anti-inflammatory activity, we looked up the decoctions that have BCT as the main herb or 君藥, and found that Chikujountanto (TJ-091) in Japanese Kampo medicine and Jukyeoondam-Tang (竹茹溫膽湯, JOT) in China[26,27] have been prescribed to relieve fever, coughing, and phlegm production caused by respiratory infection[28]. In Japan, TJ-091, equivalent to JOT, has been used to treat Covid-19 patients[29]. Collectively, the indications (適應症) or symptoms treated by these BCT-containing decoctions are related to the anti-inflammatory function of BCT. However, in Korea, similar decoctions containing BCT as the major herb seem to have different medical indications.

Korean Ministry of Food and Drug Safety (KFDA) enlists 11 different decoctions that contain BCT as a major herb; they can be categorized into 3 groups: Gwibi-tang / Hapyeoldahanso-tang (歸脾湯合熱多寒少湯), Gamiondam-tang (加味溫膽湯, GOT), and Ondam-tang (溫膽湯) (Table 1).

Table 1. Decoctions approved by KFDA that have BCT as a major herb

Prescriptions		Guibitang/Hapyeoldahanso-tang 歸脾湯合熱多寒少湯	Gamiondam-tang1* 加味溫膽湯	Gamiondam-tang 2** 加味溫膽湯	Ondam-tang 溫膽湯	Jukyeoondam-tang 竹茹溫膽湯
Herbal Constitutents	CoptisChinensis 黃連					○
	Zizyphus jujuba (Semen) 酸棗仁			○		
	Schisandra chinensis 五味子			○		
	Cyperus rotundus 香附子		○			○
	Citrus unshiu 陳皮		○	○	○	○
	Zingiber officinale 生薑		○	○	○	○
	Bupleurum falcatum 柴胡		○			○
	Pinellia ternate 半夏		○	○	○	○
	Poncirus trifoliata 枳實		○	○	○	○
	Zizyphus jujuba (Fructus) 紅棗		○		○	
	Liriope platyphylla 麥門冬		○	○		○
	Glycyrrhiza glabra 甘草	○	○	○	○	○
	Pueraria lobata 葛根	○				
	Polygala tenuifolia 遠志	○		○		
	Crataegus pinnatifida 山査	○				
	Dimocarpus longan 龍眼肉	○				
	Aucklandia lappa 木香	○				
	Angelica dahurica 白芷	○				
	Angelica gigas 當歸	○				
	Astragalus membranaceus 黃芪	○				
	Platycodon grandiflorum 桔梗	○	○			○
	Angelica tenuissima 藁本	○				
	Poria cocos 茯苓	○	○	○	○	○
	Cimicifuga heracleifolia 升麻	○				
	Scutellaria baicalensis 黃芩	○				
	Rehmannia glutinosa 熟地黃	○		○		
	Atractylodes japonica 白朮	○				
	Panax ginseng 人蔘	○	○	○		○
	Phyllostachys nigra 竹茹	○	○	○	○	○

According to KFDA, the decoctions containing BCT as a major herb can be grouped into Gwibi-tang/Hapyeoldahanso-tang(歸脾湯合熱多寒少湯), Gamiondam-tang (加味溫膽湯, GOT) 1, Gamiondam-tang (加味溫膽湯, GOT) 2, and Ondam-tang (溫膽湯). Product names, including Matrolhwan, Mega Raf Pills won jin, Bosim Anjeong hwan, Ilshim Chong myung sohwan, Chung myung Hwan, and Hansinsinmyeng hwan, belong to Gwibi-tang/Hapyeol- dahanso-tang. Kyung bang Gamiondam-tang Soft Ext. falls to Gamiondam-tang (GOT) 1, while Syntex Gamiondam-tang Ext. Granule and Jayangsimgan-tang Ext. Granule (Gamiondam-tang) do to Gamiondam-tang (GOT) 2. Hanshin Ondam-tang Ext. Granule is Ondam-tang. The herbal compositions of each group of Tang were compared side by side, along with Jukyeoondam-tang (竹茹溫膽湯, JOT). Regardless of composition, the medical indications for Gwibi-tang/Hapyeoldahanso-tang, GOT 1, GOT 2, and Ondam-tang are nervousness, amnesia, and headache. On the other hand, JOT is used to treat inflammatory pulmonary symptoms, including the pulmonary disorders caused by Covid-19 infection in Japan. The composition of JOT was referred to 萬病回春[27], and the compositions of BCT-containing decoctions were from KFDA. *Prescription of Palpitation(驚悸) in DONGUIBOGAM(東醫寶鑑) **Prescription of Insomnia Caused by Vexation of the Deficiency Type (虛煩不眠) in DONGUIBOGAM(東醫寶鑑)

Although the compositions are varied, all of them are prescribed to relieve headaches, insomnia, nervousness, or abnormal responsiveness to stimulation (erethism). Of note, the composition of GOT is almost identical to JOT, except Coptis chinesis (黃連). GOT was approved for relieving neurologic symptoms in Korea, while JOT was for inflammatory pulmonary symptoms in Japan and China. In composition, GOT contains *Z. jujuba* (Fructus), instead of *C. chinesis*. Conversely, JOT does *C. chinesis*, in the place of *Z. jujuba* (Fructus). It is noteworthy that both *Z. jujuba* (Fructus)[30] and *C. chinesis*[31] have anti-inflammatory activity. Thus, *C. chinesis* is interchangeable with *Z. jujuba* (Fructus). If taken as the case, one can say that GOT is almost identical to JOT in terms of therapeutic effect. Then, GOT may apply to treating inflammatory diseases.

Nevertheless, it remains unclear why the two decoctions, Chikujountanto or JOT and GOT are being used to treat different indications, depending on countries. These divergent applications of a BCT-containing decoction for different medical indications could be related to how Korean medicine interprets the role of BCT when formulating decoctions. Alternatively, neuronal disorders treated by GOT may be associated with neuronal inflammation, and thus both GOT and JOT target a similar, if not the same, inflammatory mechanism. However, this possibility needs to be verified by experiments. In Korea, BCT-containing decoctions seem not popular in the clinic, although precise statistical data are not available. Given the anti-inflammatory activity of BCT as a major herb and that JOT and GOT are almost identical in their compositions, it would be reasonable that the medical indications treated by GOT and other BCT-containing decoctions in Korea can be extended to treating inflammatory symptoms.

Conclusion

We presented experimental and clinical evidence supporting the anti-inflammatory function of BCT. We found that the anti-inflammatory BCT is consistent with the indications Korean medicine originally assigned to BCT. Accordant with the role of BCT, JOT, a decoction containing BCT as a major herb in Japan and China, has been used to treat inflammatory pulmonary symptoms. Although almost identical to JOT in herbal composition, GOT is approved for indications related to neurologic disorders in Korea. Given that JOT is used to treat inflammatory pulmonary disorders, we suggested that at least GOT can be repurposed to treat inflammatory symptoms, along with the approved medical indications of neurologic disorders.

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