Development of Kampo CONSORT statement in Japan

Panel session 2: Clinical Practice Guidelines development in traditional medicine in East Asia,
Guidelines International Network (G-I-N) Conference 2011,
30 August 2011, Seoul, ROK

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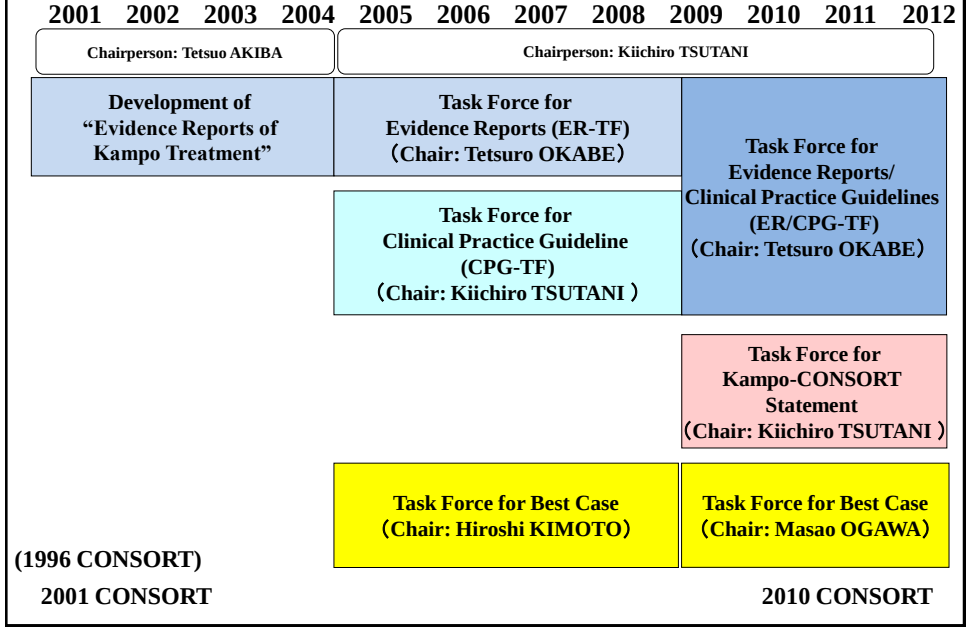
Special Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)



Needs to Kampo CONSORT statement

- **Growing awareness of CONSORT statement in Japan**
- **Software of Kampo medicine - diagnosis**
- **Hardware of Kampo medicine - substance**

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Three survey conducted

1. **Quality assessment of Kampo RCT articles**
2. **Use of Sho (証) in Kampo RCT articles**
3. **Description of substance aspect of Kampo drugs in journals in the world**

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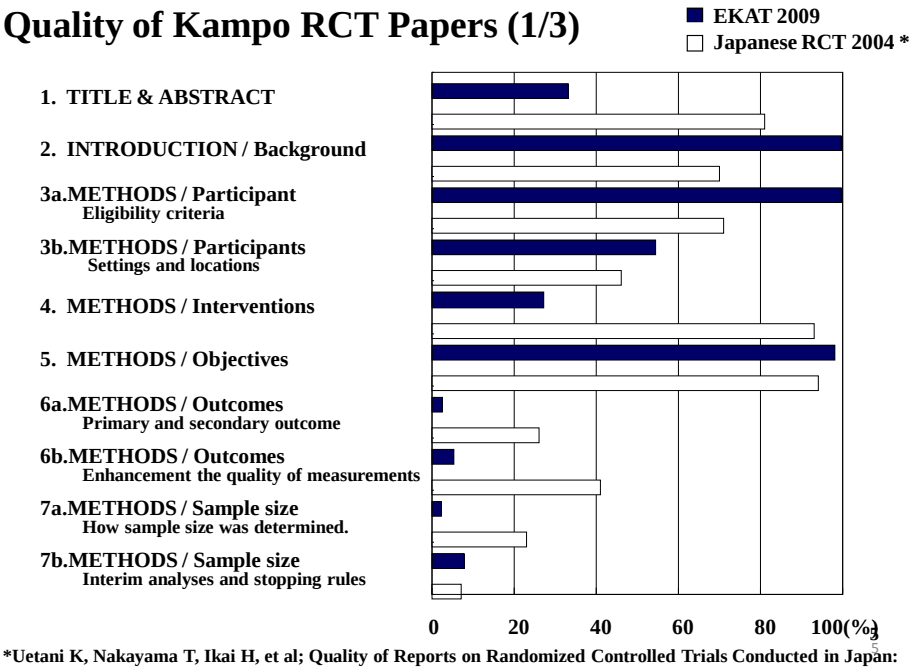
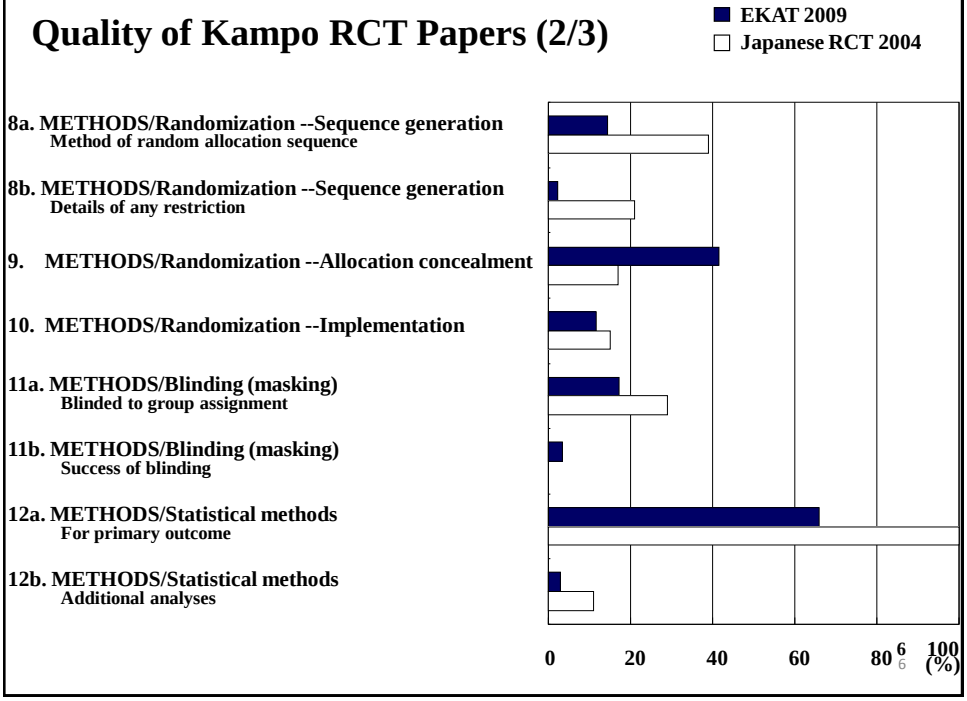
Quality of Kampo RCT Papers (1/3)

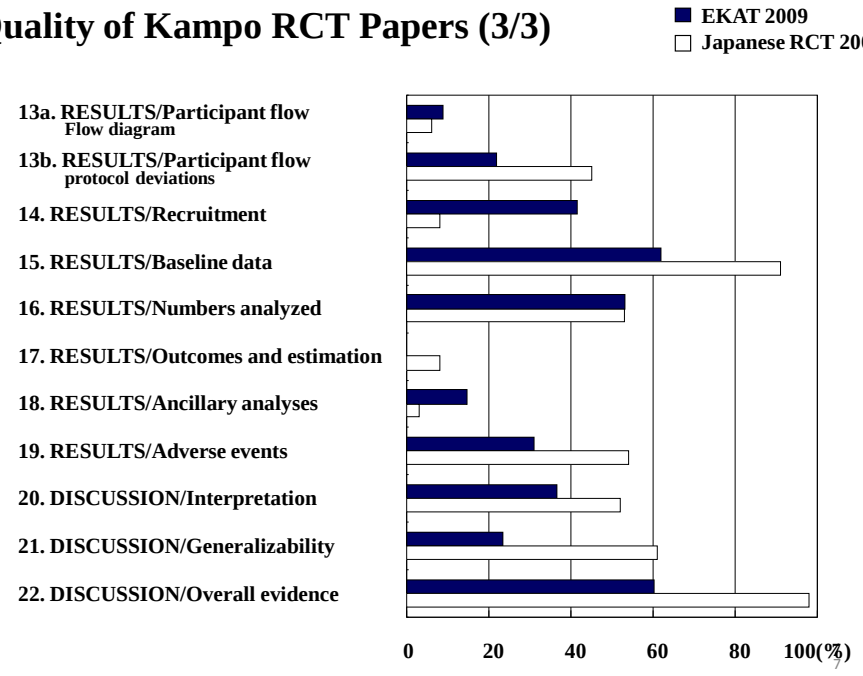


*Uetani K, Nakayama T, Ikai H, et al; Quality of Reports on Randomized Controlled Trials Conducted in Japan: Evaluation of Adherence to the CONSORT Statement. *Inter Med* 2009; 48: 307-313.

Quality of Kampo RCT Papers (2/3)



Quality of Kampo RCT Papers (3/3)



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Use of Kampo diagnosis in 345 RCTs in EKAT 2010

1. Pre-randomization

(1) Selection at entries	
Kampo concepts in inclusion criteria	**7* (2.0%)**
Kampo concepts in exclusion criteria	**9* (2.6%)**
Allocation of responder for the Kampo formulation	**3 (0.9%)**
Allocation of non-responder for the Kampo formulation	**1 (0.3%)**
(2) Selection of Kampo formulae according to Kampo criteria	**7 (2.0%)**
(3) Kampo diagnosis in background	**5 (1.4%)**

2. Post-randomization

(1) Sub-group analyses according to Kampo concepts	**24** (7.0%)**
(2) Discussion of Kampo concepts without sub-group analysis	**17 (4.9%)**
(3) Change of formulation according to Kampo diagnosis in non-responder	**1 (0.3%)**

* Both selection and exclusion criteria: 2 , ** without specific data: 4

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Kampo concept in inclusion criteria

Reference

Furue M, Tanaka Y, Kobayashi H, et al. Efficacy of Kanebo Hochuekkito in patients with atopic dermatitis with "qikyo" – a multicenter, double-blind trial*. *Arerugi* (*Japanese Journal of Allergology*). 2005; 54: 1020 (in Japanese).

Objectives

To assess the efficacy of hochuekkito (補中益気湯) for the treatment of atopic dermatitis.

Participants = Inclusion criteria

Patients with atopic dermatitis and ***"qikyo"*** **(気虚, qi deficiency)** n=77

Intervention

Arm 1: hochuekkito (補中益気湯) n=37
Arm 2: placebo n=40

Results:

Reduction of skin lesion scores : not significantly different between two arms
Changes in "qikyo" scores : not significantly different between two arms

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Kampo concepts in exclusion criteria

Reference

Nakajima O, Sone M, Kurokawa K, et al. The Complemental treatment for chronic hepatitis C. *Kagaku Ryoho Kenkyusho Kiyo* (*Bulletin of the Institute of Chemotherapy*) 2003; 34: 40-51

Objectives

To assess the efficacy of shosaikoto (小柴胡湯) for interferon-resistant chronic hepatitis C.

Participants

One hundred patients with chronic active hepatitis C who completed interferon therapy. Patients **with "in-sho" (陰証, yin pattern) and "kyo-sho" (虚証, deficiency pattern) was excluded.**

Intervention

Arm 1: squalene 1500 mg/day n=33
Arm 2: cepharanthine (1 mg/kg body weight per day) n=33
Arm 3: shosaikoto (小柴胡湯) 6.0 g/day n=34

Results:

Equivalent efficacy

Only one patient was excluded. But neither analysis nor discussion of safety. 11

Selection of Kampo formulae according to Kampo diagnosis

Reference

Ohno S. The effect of Kampo medicine on salivary secretion in Sjögren's syndrome. *Kampo to Saishin-chiryo* (*Kampo & the Newest Therapy*) 2006; 15: 134-40 (in Japanese).

Objectives

To evaluate the efficacy of Kampo medicine (as a system) for Sjögren's syndrome.

Participants

Sixty-four patients with Sjögren's syndrome.

Intervention

Arm 1: According to sho (証, pattern/syndrome) (n=32; after 2 dropped out, 30 included for analysis).
a) bakumondoto (麦門冬湯) alone or
b) bakumondoto (麦門冬湯) and rokumigan (六味丸) or
c) bakumondoto (麦門冬湯) and hachimijiogan (八味地黄丸)

"Bensho (弁証)" (Kampo diagnosis) of "jinkyo" (腎虚, kidney deficiency) which included 3 or more of the following 6 symptoms:
1) heaviness of the back; 2) heaviness in the lower legs with pain in heels and lateral surface of the lower legs; 3) tinnitus/hearing loss; 4) loss of hair and hair luster;
5) looseness or loss of teeth; 6) sexual dysfunction (impotence, nocturnal emission).

a) bakumondoto alone for negative jinkyo n=23
b) bakumondoto plus rokumigan for jinkyo without chills (冷) n= 3
c) bakumondoto plus hachimijiogan for jinkyo with chills (冷) n= 4

Arm 2: hochuekkito (補中益気湯) (n=32; after 4 dropped out, 28 included for analysis).

Main results

The amount of increase in salivary secretions in Arm 1 was significantly greater than Arm 2 ($p<0.005$). 12

Sub-group analyses according to Kampo concepts

Reference

Miyamoto T, Inoue H, Kitamura S, et al. Effect of TSUMURA Sho-seiryu-to (TJ-19) on bronchitis in a double-blind placebo-controlled study. *Rinsho Iyaku* (*Journal of Clinical Therapeutics & Medicine*) 2001; 17: 1189-214

Objectives

To evaluate the efficacy and safety of shoseiryuto (小青竜湯) in the treatment of bronchitis.

Participants

Patients with mild to moderate bronchitis, and evaluable symptoms

Intervention

Arm 1: Shoseiryuto (小青竜湯) n=101
Arm 2: placebo n= 91

Results

Trend of moderate-to-marked global improvement in Arm 1 than Arm 2

Subgroup analyses

In patients without physical frailty; and those with cough and watery sputum showed a significantly higher rate of global improvement in arm 1 than arm 2.

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Items to be used for Kampo medicine RCTs in CONSORT statement

- **Software of Kampo medicine - diagnosis**
  - **4a: eligibility criteria (inclusion criteria and exclusion criteria)**
  - **5: Intervention**
- **Hardware of Kampo medicine - substance**
  - **5: Intervention**

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Three survey conducted

1. **Quality assessment of Kampo RCT articles**

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3. **Description of substance aspect of Kampo drugs in journals in the world**

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Survey of description of substance aspect of Kampo drug

- **Surveyed journals**
  - ***Journal of Traditional Medicine***
  - ***The American Journal of Chinese Medicine***
  - ***Phytomedicine***
  - ***Journal of the American Geriatrics Society***
  - ***Journal of Ethnopharmacology***
  - ***Phytotherapy Research***
  - ***Planta Medica***

- **Various styles exist**

  Detailed description needs more than one page of the study paper.

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Policy

- **Develop independent website in stead of describing everything in an article**
- **Focus on marketed ethical 148 Kampo drugs in Japan**
- **In cooperation with Research Center for Medicinal Plant Resources (RCMPR), National Institute of Biomedical Innovation (NIBIO, 独立行政法人医薬基盤研究所 薬用植物資源研究センター)**

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Substance aspect of Kampo drugs

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Herbal “drug” products in Japan

(2005, US$ mil)

	Ethical	OTC/others	Total
520 Kampo drug	884	150	1,033
510 Crude herbal product	22	9	30
590 Finished herbal product	13	41	54
Total	918	200	1,119

（US$1=100yen）

Source: Japan Kampo Medicines Manufactures Association (JKMA) (ed.). “Production of Herbal drug products” (15 Jan 2009) [Original source: MHLW. Annual Report of Pharmaceutical Production in Japan 2005]

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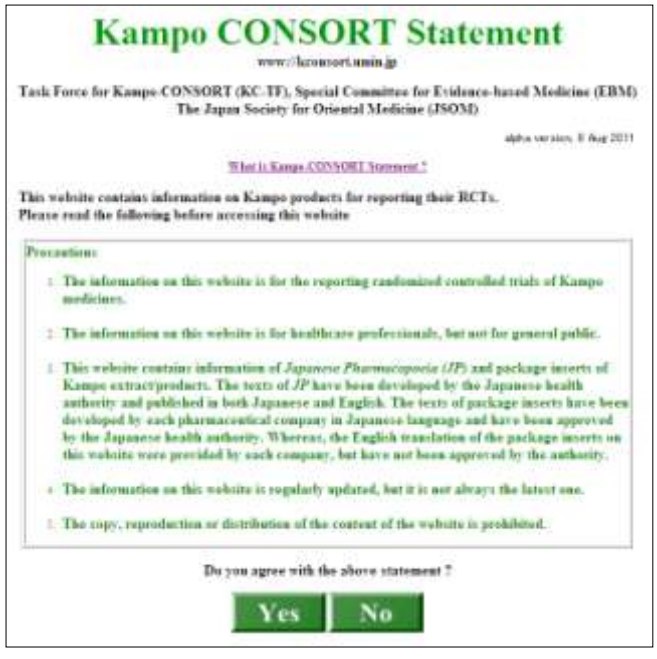

http://kconsort.umin.jp/

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Twenty one Kampo Extracts are included in the Japanese Pharmacopoeia (日本薬局方)

JP15 (April 2006) 6

- 葛根湯 (kakkonto)
- 大黄甘草湯 (daiokanzoto)
- 加味逍遙散 (kamishoyosan)
- 苓桂朮甘湯 (ryokeijutsukanto)
- 補中益気湯 (hochuekkito)
- 柴苓湯 (saireito)

JP15 Supplement 1 (October 2007) 2

- 半夏厚朴湯 (hangekobokuto)
- 桂枝茯苓丸 (keishibukuryogan)

(change: 4)

JP15 Supplement 2 (October 2009) 2

- 八味地黄丸 (hachimijiogan)
- 真武湯 (shimbuto)
- 牛車腎気丸 (goshajinkigan)

(change: 4)

JP16 (April 2011) 11

- 黄連解毒湯 (orengedokuto)
- 柴胡桂枝湯 (saikokeishito)
- 柴朴湯 (saibokuto)
- 十全大補湯 (juzentaihoto)
- 小柴胡湯 (shosaikoto)
- 小青竜湯 (shoseiryuto)
- 大建中湯 (daikenchuto)
- 釣藤散(choreito)
- 麦門冬湯(bakumondoto)
- 六君子湯 (rikkunshito)
- 芍薬甘草湯 (shakuyakukanzoto)

Table of the Links of Kampo Product informations in Japanese Pharmacopoeia (JP) and/or Package Insert

Task Force for Kampo CONSORT (KC-TF), Special Committee for Evidence based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

alpha version, 9 Aug. 2011

No.	Name in Roman Alphabet	Name in Han Character	Japanese Pharmacopoeia (JP)				Package Insert (in Japanese)
			Previous version (in English)			Present version (in Japanese)	
			JP XV (2006)	JP XV Suppl. I (2007)	JP XV Suppl. II (2009)	JP XVI (2011)	
19	daiokanzoto	大黄甘草湯	✓		✓	✓	ja
20	daisaikoto	大柴胡湯					ja
21	daisaikotokyokkato	大柴胡湯去大黄					
22	eppikajutsuto	越脾加朮湯					ja
23	gikyoto	五虎湯					ja
24	goreisan	五苓散					ja
25	gorinsan	五淋散					ja
26	gosha jinkigan	牛車腎気丸			✓	✓	ja
27	gotokosan	五積散					ja
28	goshuyuto	呉茱萸湯					ja
29	hachimijiogan	八味地黄丸			✓	✓	ja
30	hainosankyuto	排膿散及湯					ja
31	hangebyakujutsutemmato	半夏白朮天麻湯					ja
32	hangekobokuto	半夏厚朴湯		✓		✓	ja
33	hangeshashinto	半夏瀉心湯					ja
34	heikoto	平胃散					ja
35	hochuekkito	補中益気湯	✓	✓	✓	✓	ja
36	hochigoreisan	四苓五香散					ja

Daikenchuto Extract (大甘草湯エキス)

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JP XV (2006)

Daikenchuto Extract (大甘草湯エキス)

Marker, Method of preparation, Description, Identification, Purity, and others

Daiokanzoto Extract

大黄甘草湯エキス

Daiokanzoto Extract contains not less than 3.5 mg and not more than 10.5 mg of sennoside A ($C_{42}H_{38}O_{20}$: 862.74) and not less than 9 mg and not more than 27 mg (for preparation prescribed 1 g of Glycyrrhiza) or not less than 18 mg and not more than 54 mg (for preparation prescribed 2 g of Glycyrrhiza) of glycyrrhizic acid ($C_{42}H_{62}O_{16}$: 822.93) per a dried extract prepared as directed in the Method of preparation.

Method of preparation Prepare a dried extract as directed under Extracts, with 4 g of Rhubarb and 1 g of Glycyrrhiza, or with 4 g of Rhubarb and 2 g of Glycyrrhiza.

Description Daiokanzoto Extract occurs as a brown powder. It has a characteristic odor and an astringent first then slightly sweet taste.

Identification (1) Rhubarb—To 1.0 g of Daiokanzoto Extract add 10 mL of water, shake, then add 10 mL of diethyl ether, shake, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 1 mg of rhein for thin-layer chromatography in 1 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography ⟨2.03⟩. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol and water (20:3:2) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the spot among the several spots from the sample solution has the same color tone and *Rf* value with the orange fluorescent spot from the standard solution.

(2) Glycyrrhiza—To 0.5 g of Daiokanzoto Extract add 10 mL of water, shake, then add 10 mL of 1-butanol, shake, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 1 mg of liquiritin for thin-layer chromatography in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography ⟨2.03⟩. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol and water (20:3:2) to a distance of about 10 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat at 105°C for 5 minutes: one of the spot among the several spots from the sample solution has the same color tone and *Rf* value with the yellow-brown spot from the standard.

Purity (1) Heavy metals ⟨1.07⟩—Prepare the test solution with 1.0 g of Daiokanzoto Extract as directed in (4) in Extracts under the General Rules for Preparations, and perform the test (not more than 30 ppm).

(2) Arsenic ⟨1.11⟩—Prepare the test solution with 0.67 g of Daiokanzoto Extract according to Method 3, and perform the test (not more than 3 ppm).

Loss on drying ⟨2.41⟩ Not more than 7.0% (1 g, 105°C, 5 hours).

Total ash ⟨2.44⟩ Not more than 10.0%.

....

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Suppl II, JP XV (2009)

Daiokanzoto Extract

大黄甘草湯エキス

Change the Origin to read:

Daiokanzoto Extract contains not less than 3.5 mg of sennoside A ($C_{42}H_{38}O_{20}$: 862.74) and not less than 9 mg and not more than 27 mg (for preparation prescribed 1 g of Glycyrrhiza) or not less than 18 mg and not more than 54 mg (for preparation prescribed 2 g of Glycyrrhiza) of glycyrrhizic acid ($C_{42}H_{62}O_{16}$: 822.93) per the extract prepared as directed in the Method of preparation.

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English translation is under preparation

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27	gorokusan	五積散					
28	goshuyuto	呉茱萸湯					
29	hachimijiogan	八味地黄丸			✓	✓	
30	hainosankyuto	排膿散及湯					
31	hangebyakujutsutemmatto	半夏白朮天麻湯					
32	hangekobokuto	半夏厚朴湯		✓		✓	
33	hangeshashinto	半夏瀉心湯					
34	hekisan	平胃散					
35	hochuekkito	補中益気湯	✓	✓	✓	✓	
36	hochugoreisan	四苓五苓散					

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Revised: May 2007 (4th version)

Standard Commodity Classification No. of Japan
875209

- Kampo-preparation-

TSUMURA Daiokanzoto Extract Granules for Ethical Use

-daiokanzoto-

Storage
Store in light-resistant, air-tight containers

Expiration date
Use before the expiration date indicated on the container and the outer package

Approval No.	01AM5519
Date of listing in the NHI reimbursement price	October 1996
Date of initial marketing in Japan	October 1996
Date of latest revaluation	March 1996

DESCRIPTION

Composition	7.5 g of TSUMURA Daiokanzoto extract granules contains 1.5 g of a dried extract of the following mixed crude drugs: JP Rhubarb ..... 4.0 g; JP Glycyrrhiza ..... 2.0 g (JP: The Japanese Pharmacopoeia)	
	Inactive ingredient	JP Magnesium Stearate; JP Lactose Hydrate
Description	Dosage form	Granules
	Color	Yellow-brown
	Smell	Characteristic smell
	Taste	Slightly sweet and astringent
	ID code	TSUMURA 84

2. Important Precautions

(1) When this product is used, the patient's [redacted] constitution(symptoms) should be taken into account. The patient's progress should be carefully monitored, and if no improvement in symptoms/findings is observed, continuous treatment should be avoided.

(2) Since this product contains Glycyrrhiza, careful attention should be paid to the serum potassium level, blood pressure, etc., and if any abnormality is observed, administration should be discontinued.

(3) When this product is coadministered with other Kampo-preparations (Japanese traditional herbal medicines) etc., attention should be paid to the duplication of the contained crude drugs. Special caution should

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Future Plan

- **Authors are requested to write:**
  http://kconsort.umin.jp
- **First version will be loaded in 2012**
- **Link to individual ingredient to the database at RCMPR/NIBIO**
- **Link to genetic information of individual ingredient at RCMPR/NIBIO**

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Acknowledgements

Kampo CONSORT Task Force

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Thank you

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