A Proposal of Dietary Supplement from Choto-san, a Kampo Medicine

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I. *Introduction*

HERBAL medicines were first introduced to Japan by a Chinese monk "Ganjin wajo" in 5 AC. Since then, various Chinese herbal medicines together with the medical treatment system, which had been developed in Han and the following dynasty of China, were transmitted to Japan for over 1,000 years. Since then, traditional Chinese medicine which used herbal medicines developed as the Kampo medicine in Japanese own way.

Choto-san (Gouteng-san in Chinese) is one of the prescriptions in Kampo medicine, which consists of ten medicinal herbs and gypsum fibrosum (Table 1). The original indication of Choto-san is for chronic headache and hypertension. Target group of patients based on the Kampo medicine is as follows: to considerably built patients of middle age with weak physical constitution, chronic headache, painful tension of the shoulder and cervical muscle, vertigo, morning headache, heavy feeling of the head, feeling of uprising heat, tinnitus, and insomnia.

Table 1 Choto-san: Composition, Kampo Diagnosis, Indication and Usage

Constituents Item	Component herb	Constituents (Indicator)

Choto-san	Hook of *Uncaria sinensis* (Oliv.) Havil. (3)	idole alkaloids
	Uncaria rhynchophylla	polyphenols, tannins
(Gouteng-san)	Peel of*Citrus unshiu* Mare. (3)	D-limonen, hesperdin
		(essential oils)
	Tuber of *Pinellia ternata* Breit. (3)	homogentisic acid
	Root of *Ophiopogon japonicus* Ker-Gawler (3)	ophiopogonin A, B
	Poria cocos (Fr.) Wolff (3)	pachyman
	Root of *Panax ginseng* C.A.Meyer (2)	ginsenosides
	Flower of *Chrysanthemum morifolium* Hemsl. (2)	
	Root of *Ledebouriella seseloides* Woll. (2)	psolaren, deltoin
	Gypsum CaSO4□ 2H2O (5)	calcium
	Root of *Glycyrrhiza uralensis* (1)	glycyrrhizin
	Tuber of *Zingiber officinale* Roscoe (1)	zingiberene
Kampo diagnosis	Yang-disease 2 stage, Yang-deficiency, Oketsu type, KI-deficiency	
Indication	Chronic headache and hypertension	
Usage	4.5 g/day, p.o. (divided into two to three times)	

Note: Numeral in the parentheses indicates weight of dried herbs (gram) which is used to make decoction every day. A mixture of herbs are decocted with hot water and patients drink the extract three times a day prior to the meal.

II. *Clinical efficacy of Choto-san in patients with vascular dementia and the aim of the pharmacological study*

The clinical efficacy of Choto-san was examined by the double blind and placebo controlled study. Choto-san (4.5 g/day, p.o.) and a placebo were each given three times a day to a group of patients with vascular dementia for 12 weeks. Choto-san was statistically superior to the placebo in global improvement rating (GIR), utility rating, GIR of subjective symptoms (heaviness of head, headache, dizziness of vertigo, etc.), GIR of psychiatric symptoms (spontaneity, emotion, intellectual ability, etc.) and GIR of disturbance in daily living activities (sitting, standing, walking, washing face and hands, etc.) at the end of 12 weeks administration. While, GIR of neurological symptoms (aphagia, dysarthria, motor disturbance, etc.) was not significantly different from the placebo at the evaluation points (Terasawa et al., 1997).

To clarify the clinical efficacy, effects of Choto-san, a major component herb Choto-ko (*Uncaria sinensis* and *U. rhychophylla*) and the constituents were investigated in various pharmacological models.

III. *Animal model for vascular dementia: ischemia-induced impairment of spatial memory in mice*

The spatial memory and learning ability of mice exposed to transient cerebral ischemia were studied in water maze performance. The mice with the cerebral ischemia took a longer time to find the hidden platform than the sham-operated control during the learning trials in the water maze test, although the ischemia did not affect the swimming ability of the mice in the pretraining trial.

Pretreatment of mice with Choto-san (750 - 6,000 m/kg, p.o.), Chotoko (75 - 600 mg/kg), both the alkaloid fraction (188 mg/kg) and the phenolic fraction (188 mg/kg) of Chotoko, or indole alkaloids rhynchophylline (10 mg/kg) and geissoschizine methylether (10 mg/kg) prior to the ischemia shortened significantly the latency of ecaping onto the platform during the learning

period for 5 days and significantly increased the time of crossing the former platform quadrant in the probe trial on the 6th day after the transient ischemia as compared with the ischemic control, respectively. A reference agent, tacrine (1 and 2.5 mg/kg, i.p.), significantly shortened the latency of escaping onto the the platform in the water maze performance.

IV. *Multi-action mechanisms (1): anti-hypertenstive effects in SHR-SP*

The subchronic administration of Choto-san at a dose of 0.5 or 5 g/kg/day, p.o., or Chotoko at a dose of 0.05 g/kg/day, p.o., produced a significant hypotensive effects and a tendency to inhibit the induction rate of the apoplexy in SHR-SP. While Saiko-keishi-to (0.5 and 5.0 g/kg/day, p.o.), another Kampo medicine of the negative control, affected neither the blood pressure nor the apoplexy. The subchronic administration of a reference agent, nicardipine, produced prominent hypotensive effect at doses 1 and 10 mg/kg/day, p.o., and inhibition of apoplexy at 10 mg/kg/day, p.o.

V. *Multi-action mechanisms (2): an indicrect mechanism -- anti-oxidant and anti-lipid peroxidation in vitro*

Application of hydrogen peroxide to NG 108-15 cells *in vitro* significantly reduced the cell viability in a concentration-dependent manner with an IC_{50} of 500 uM. Prior application of Choto-san (250 - 1,000 ug/ml), Chotoko (250 - 1,000 ug/ml) and the consitituents of Choto-ko, (-) epicatechin and caffeic acid (200 uM), to 500 uM of hydrogen peroxide significantly inhibited the reduction of the cell viability as compared to that of the control treated with H2O2 alone. A reference immunosuppressive ligand FK506 (100 - 1,000 nM) prominently inhibited the H2O2-induced reduction of the cell viability in a concentration-dependent manner.

In the brain homogenate, Choto-san, methanol extract of Chotoko, (-)epicatechin and a reference agent of vitamin E showed a significant anti-lipid peroxidation activity with IC_{50} values of 124.7 ug/ml, 4.6 ug/ml, 39.3 uM and 153.7 uM, respectively.

VI. *Muti-action mechanisms (3): drug-receptor interactions -- Inhibition of NMDA receptor function with indole alkaloids*

To clarify possible mechanism(s) underlying actions of Choto-san and/or Choto-ko, effects of indole alkaloids isolated from *Uncaria rhynchophylla* on NMDA receptor function using a receptor expression model of *Xenopus oocytes* were investigated. Rhynchophylline and isorhynchophylline (1 - 100 uM) per se did not induce membrane current, but reversibly reduced N-methyl-D-aspartate (NMDA)-induced current in a cocentration-dependent but not voltage-dependent manner. The IC_{50} values of rhynchophylline and isorhynchophylline were of 43.2 and 48.3 uM, respectively. While, those alkaloids produced no effect on the current mediated either by ionotropic kainic acid-type and (+)-*alpha*-3-hydorxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptors or by the metabotropic glutamate receptor 1 and 5. The alkaloids (30 uM) significantly reduced the maximal current response evoked by NMDA and glycine (co-agonist of NMDA receptor), but had no effect on the EC_{50} values and Hill coefficients of NMDA and glycine for inducing currents.

VII. A proposal of a new dietary supplement from Choto-ko

Pharmacological profile of Choto-san, a Kampo medicine, is quite similar to that of a component herb Choto-ko. Thus, it is possible to prepare a new medicine or a supplement from Choto-ko after eliminating unnecessary substances (tannins, saponosides, coumarins) and concentrating active substances (flavonoids and alkaloids) considered to be relevant to clinical efficacy. The extraction procedure and the chemical definition of the extract should be controlled and standardized.

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