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Efficacy of Choto-san on vascular dementia

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Abstract

Multi-center, well-controlled and double-blind study were carried out to evaluate the efficacy of Choto-san (釣藤散) extract (7.5 g/day) in comparison with a placebo, each given three times a day for 12 weeks to patients suffering from vascular dementia. In a well-controlled study, 60 patients with a mean age of 78.9 years were enrolled and analyzed. Choto-san was superior to the placebo with statistical significance in global improvement rating, utility rating, global improvement rating of subjective symptoms, global improvement rating of psychiatric symptoms and global improvement rating of disturbance in daily living activities. In a double-blind study, with more objective criteria than a well-controlled study, 139 patients with a mean age of 76.6 years were enrolled and analyzed, Choto-san was superior to the placebo with statistical significance in global improvement rating, utility rating, global improvement rating of subjective symptoms, global improvement rating of psychiatric symptoms and global improvement rating of disturbance in daily living activities. These results suggest that Choto-san is effective in the treatment of vascular dementia.

Key words Choto-san, vascular dementia, well-controlled study, double-blind study.

Abbreviations Choto-san (Diao-Teng-San), 釣藤散 ; DSM-III-R, Diagnostic and statistical manual of mental disorder (Third edition-revised) ; HDS-R, Revised version of Hasegawa's dementia scale.

Introduction

Together with the prolongation of the average life span, the accompanying cerebrovascular disorders and dementia have become social problems, and effective therapy for vascular dementia has been anticipated.

Traditionally in Oriental medicine, Choto-san (釣藤散) has been administered to relatively aged patients with physical weakness and such subjective symptoms as headache, dizziness, vertigo, tinnitus, shoulder stiffness and so forth. In recent years, clinical studies that revealed the efficacy of Choto-san on tinnitus,[1] vertigo and dizziness[2] and so on, have been carried out in Japan. Many of these symptoms are thought to originate from disorders in the cerebrovascular system. Furthermore, Yamamoto[3] reported that Choto-san was effective in the treatment of Alzheimer type dementia.

We therefore believed that Choto-san might have the capability of improving vascular dementia and the accompanying symptoms. So, for the purpose of evaluating the efficacy of Choto-san on vascular dementia objectively, we set out to perform a multi-center, well-controlled, Choto-san versus placebo, study.[4] Furthermore, to evaluate its efficacy using more objective criteria, we carried out a multi-center, double-blind study.[5]

A well-controlled study[4]

Patients and Methods

Patient selection : Patients diagnosed as vascular dementia were selected according to the following criteria.

1) Patients were defined according to the criteria of DSM-III-R,[6] their Carlo Loeb modified ischemic

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scores [7] were 5 points or more, and their general condition was stable.

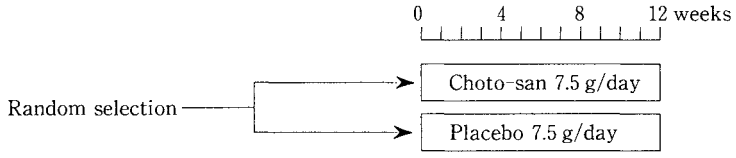
2) One month or more had passed since the last stroke such as cerebral infarction, cerebral bleeding, subarachnoidal bleeding, *etc.*

3) Patients with dementia of Alzheimer type, severe dementia, complicated by other severe diseases, and judged to be inappropriate for this study by the investigators, were excluded from entry into this trial.

Informed consent was obtained from the patients and/or their families prior to enrollment in this trial.

Methods: Study protocol was shown in Fig. 1. This study was designed by the controller (Dr. Takaori, President of Shimane Medical University), and was planned as a multi-center, placebo-well-controlled, inter-patient trial. Patients were randomly selected to be administered either Choto-san extract (TJ-47, Tsumura & Co., 7.5 g/day) or matched placebo after meals three times a day for 12 weeks. The placebo used in this study was made by Tsumura & Co., consisted of lactose, dextrin, maltose, cellulose, hydroxypropyl cellulose, magnesium stearate, colorants and flavors, and could not be distinguished from the active drug in form, color tone and taste by a number of examiners before this trial. Moreover, it was guaranteed by the controller that discrimination between the active drug and the placebo used in this study was impossible. During the trial, no other major new medication was allowed.

Patient characteristics were assessed and brain computed tomography was done before entry. Global severity rating, the global severity ratings of subjective symptoms, neurological symptoms, psychiatric symptoms and disturbance in daily living activities, as well as the severity rating of each symptom were evaluated by the investigators at the beginning, and after 4, 8 and 12 weeks of medication by means of a 5-point rating scale (0=no symptom, 1=very slightly affected, 2=slightly affected, 3=moderately affected, 4=severely affected). The respective symptoms evaluated are described in Table I. Global improve-



Patient characteristics	○			
Brain computed tomography or magnetic resonance imaging*	○			
Global severity rating	○	○	○	○
Global improvement rating		○	○	○
Overall safety rating				○
Utility rating				○
Global severity rating of subjective symptoms	○	○	○	○
Global improvement rating of subjective symptoms		○	○	○
Global severity rating of neurological symptoms	○	○	○	○
Global improvement rating of neurological symptoms		○	○	○
Global severity rating of psychiatric symptoms	○	○	○	○
Global improvement rating of psychiatric symptoms		○	○	○
Global severity rating of disturbance in daily living activities	○	○	○	○
Global improvement rating of disturbance in daily living activities		○	○	○
Severity rating of each symptom	○	○	○	○
Improvement rating of each symptom		○	○	○
Revised version of Hasegawa's dementia scale	○	○	○	○
Laboratory tests	○	△	△	○

*Only brain computed tomography was examined in a well-controlled study.
○ : assessed necessarily ; △ : assessed as much as possible

Fig. 1 Study protocol.

Table I Symptoms evaluated in the study.

- Subjective symptoms
  - Heaviness of head
  - Headache
  - Dizziness or vertigo
  - Shoulder stiffness
  - Palpitation
  - Distress feeling of chest
  - Feeling of hot flushes
  - Tinnitus
  - Numbness of limbs
  - Coldness of limbs
  - General malaise
  - Appetite loss
- Neurological symptoms
  - Aphasia
  - Dysarthria
  - Motor disturbance
  - Tremor
  - Rigidity
  - Sensory disturbance
  - Urinary incontinence
- Psychiatric symptoms
  - Spontaneity
    - Expression of intentions
    - Interest in television or books
    - Interest in housework or rehabilitaion
    - Conversation
    - Global spontaneity
  - Emotion
    - Lack of facial expression
    - Bad humor
    - Depressed mood
    - Emotional incontinence
    - Anxiety
    - Global emotion
  - Intellectual ability
    - Disorientation
    - Disturbance in short-term memory
    - Disturbance in long-term memory
    - Decline in simple arithmetic ability
    - Global intellectual ability
  - Abnormal behavior
    - Hyperkinesia or wandering
    - Restlessness or excitement
    - Nocturnal delirium
    - Global abnormal behavior
  - Sleep disturbance
  - Hallucination or delusion
- Disturbance in daily living activities
  - Sitting
  - Standing
  - Walking
  - Washing face and hands
  - Putting on and taking off clothes
  - Having meals regularly
  - Excretion
  - Bathing

ment rating, the global improvement ratings of subjective symptoms, neurological symptoms, psychiatric symptoms and disturbance in daily living activities, as well as the improvement rating of each symptom were evaluated after 4, 8 and 12 weeks of medication by means of a 6-point rating scale (I=remarkable improvement, II=moderate improvement, III=slight improvement, IV=unchanged, V=aggravation, VI=no symptom both at the beginning and at the point of evaluation). Furthermore, the overall safety and utility ratings were also evaluated at the end of the study. HDS-R [8] was assessed by the investigators at the beginning, and after 4, 8 and 12 weeks of medication. In addition, routine laboratory tests were performed at the beginning and the end of the study.

Results

The total enrollment consisted of 60 patients, 9 males and 51 females, and the mean age (±S.D.) was 78.9±7.6. The Choto-san group consisted of 32 cases and the placebo group 28 cases.

Patient characteristics were shown in Table II. There was no statistical difference between the Choto-san and placebo groups in terms of sex, age, duration of dementia, causal disease of dementia, complications, rehabilitation, concomitant drugs and results of the brain computed tomography.

Global improvement rating was shown in Table III. Choto-san was superior to placebo with statistical significance in the global improvement rating for each evaluating point at 4 weeks ($p<0.05$), 8 weeks ($p<0.01$) and 12 weeks ($p<0.01$).

Subjective symptoms: Choto-san was superior to placebo with statistical significance in the global improvement rating of subjective symptoms for each evaluating point at 4 weeks ($p<0.05$), 8 weeks ($p<0.01$) and 12 weeks ($p<0.01$) (Table III). Choto-san was superior to placebo with statistical significance in the improvement rating of such subjective symptoms as dizziness or vertigo at 4 weeks ($p<0.05$), shoulder stiffness at 4 weeks ($p<0.05$) and 12 weeks ($p<0.05$), and palpitation at 12 weeks ($p<0.05$).

Neurological symptoms: There was no statistically significant difference between the Choto-san and placebo groups in the global improvement rating of neurological symptoms at any of the evaluation points (Table III). Choto-san was inferior to placebo with

Table II Patient characteristics in a well-controlled study.

	Total	Choto-san	Placebo	
Sex				N.S.[a]
Male	9	6	3	
Female	51	26	25	
Age (year)	78.9±7.6	80.3±5.5	77.3±9.2	N.S.[b]
Duration of dementia (months)	47.5±48.6	41.6±33.2	54.6±61.4	N.S.[b]
Causal disease				N.S.[a]
Cerebral infarction	59	32	27	
Cerebral bleeding	0	0	0	
Subarachnoidal hemorrhage	1	0	1	
Complication				N.S.[a]
None	9	4	5	
Hypertension	33	18	15	
Ischemic heart disease	13	5	8	
Diabetes mellitus	3	2	1	
Parkinson syndrome	3	2	1	
Liver disease	2	1	1	
Renal disease	1	0	1	
Others	21	12	9	
Rehabilitation				N.S.[a]
Doing	21	11	10	
Not doing	39	21	18	
Concomitant drugs				N.S.[a]
Cerebral circulation improver	7	4	3	
Cerebral metabolic activator	5	3	2	

a : Chi-square test, b : Mann-Whitney test
Values present the mean±S.D.

Table III Global improvement rating in a well-controlled study.

	4 weeks	8 weeks	12 weeks
Patients number at each evaluation point			
Choto-san	31	31	31
Placebo	26	26	26
Global improvement rating			
Choto-san	0:2:9:20:0	0:4:15:11:1	0:8:14:8:1
Placebo	0:0:4:19:3	0:0:5:18:3	0:2:4:15:5
	$p<0.05$	$p<0.01$	$p<0.01$
Global improvement rating of subjective symptoms			
Choto-san	0:1:12:14:3	0:3:14:10:2	0:5:11:9:4
Placebo	0:0:4:16:4	0:0:5:11:8	0:0:5:9:10
	$p<0.05$	$p<0.01$	$p<0.01$
Global improvement rating of neurological symptoms			
Choto-san	0:0:0:20:0	0:0:1:18:1	0:0:3:16:2
Placebo	0:0:1:15:0	0:0:2:14:0	0:0:4:12:0
	N.S.	N.S.	N.S.
Global improvement rating of psychiatric symptoms			
Choto-san	0:3:10:17:1	0:1:17:10:3	0:2:16:10:3
Placebo	0:0:4:17:4	0:0:3:15:7	0:1:5:10:9
	$p<0.05$	$p<0.01$	$p<0.01$
Global improvement rating of disturbance in daily living activities			
Choto-san	0:0:4:19:1	0:1:6:15:2	0:1:8:14:1
Placebo	0:0:0:14:3	0:0:2:11:4	0:0:3:8:5
	$p<0.05$	N.S.	$p<0.05$

Values of Choto-san and placebo present the number of patients evaluated as remarkable improvement : moderate improvement : slight improvement : unchanged : aggravation, respectively.
Others were evaluated as no symptom. p value : Mann-Whitney test.

statistical significance in the improvement rating of urinary incontinence at 8 weeks ($p<0.05$) and 12 weeks ($p<0.05$).

Psychiatric symptoms : Choto-san was superior to placebo with statistical significance in the global improvement rating of psychiatric symptoms at 4 weeks ($p<0.05$), 8 weeks ($p<0.01$) and 12 weeks ($p<0.01$) (Table III). Choto-san was superior to the placebo with statistical significance in the improvement rating of such psychiatric symptoms as decline in interest in television or books at 8 weeks ($p<0.05$) and 12 weeks ($p<0.05$), lack of facial expression at 12 weeks ($p<0.05$) and disorientation at 4 weeks ($p<0.05$).

Disturbance in the daily living activities : Choto-san was superior to placebo with statistical significance in the global improvement rating of disturbance in daily living activities at each evaluating point at 4 weeks ($p<0.05$) and 12 weeks ($p<0.05$) (Table III). Choto-san was superior to the placebo with statistical significance in the improvement rating in the disturbance of excretion at 4 weeks ($p<0.05$).

HDS-R : In the Choto-san group, the mean HDS-

Rs of all evaluation points at 4 weeks (16.65±4.43) ($p<0.05$), 8 weeks (17.94±4.79) ($p<0.01$) and 12 weeks (19.39±5.71) ($p<0.01$) were higher than that at the beginning of this study (15.34±3.76) with statistical significance. On the other hand, in the placebo group, there was no statistical significance between the mean HDS-R at the beginning (14.89±3.84) and those at all the evaluation points at 4 weeks (16.42±5.25), 8 weeks (15.81±5.82) or 12 weeks (16.50±5.97). Between the mean HDS-Rs of the Choto-san and placebo groups, there was no statistical significance at any of the evaluation points of 4, 8, or 12 weeks.

Overall safety rating : There was no statistical significance between the Choto-san and placebo groups in terms of overall safety rating. One Choto-san case suffered from adverse effects and medication was stopped. With the discontinuation of medication, the elevated levels AST and ALT returned to normal. Another Choto-san case suffered a slight decrease in the serum potassium level, but medication was continued. In all the other cases, there were no negative changes in laboratory data that could be attributed to the administration of Choto-san or placebo by the investigators.

Table IV Utility rating in a well-controlled study.

	Very useful	Useful	Slightly useful	Useless	Harmful
Choto-san	2	12	11	6	1
Placebo	0	2	5	17	4

$p<0.01$: Mann-Whitney test

Utility rating (Table IV) : Choto-san was superior to placebo in the utility rating with statistical significance ($p<0.01$).

A double-blind study[5)]

Patients and Methods

Criteria of patient selection and methods were the same as in the previous well-controlled study.[4)]

Table V Patient characteristics in a double-blind study.

	Total	Choto-san	Placebo	
Sex				N.S.[a]
Male	50	28	22	
Female	89	41	48	
Age (year)	76.6±8.4	75.7±8.9	77.6±7.9	N.S.[b]
Duration of dementia (months)	23.6±18.8	23.7±20.0	23.5±17.6	N.S.[b]
Causal disease				N.S.[a]
Cerebral infarction	127	61	66	
Cerebral bleeding	9	6	3	
Subarachnoidal hemorrhage	1	1	0	
Others	2	1	1	
Complication				N.S.[a]
Hypertension	75	41	34	
Ischemic heart disease	37	17	20	
Diabetes mellitus	11	6	5	
Parkinson syndrome	7	3	4	
Liver disease	2	1	1	
Renal disease	1	0	1	
Others	54	27	27	
Rehabilitation				N.S.[a]
Doing	59	30	29	
Not doing	80	39	41	
Concomitant drugs				N.S.[a]
Not administering	18	6	12	
Administering	121	63	58	

a : Fisher's exact probability test, b : Mann-Whitney test
Values present the mean±S.D.

Results

The total enrollment consisted of 139 patients, 50 males and 89 females, and the mean age (±S.D.) was 76.6±8.4. The Choto-san group consisted of 69 cases and the placebo group 70 cases.

Patient characteristics were shown in Table V. There was no statistical difference between the Choto-san and placebo groups in terms of sex, age, duration of dementia, causal disease of dementia, complications, rehabilitation and concomitant drugs.

Global improvement rating was shown in Table VI. Choto-san was statistically superior to the placebo in global improvement rating at 8 weeks ($p<0.01$) and 12 weeks ($p<0.001$).

Subjective symptoms : Choto-san was superior to placebo with statistical significance in the global improvement rating of subjective symptoms for evaluating point at 8 weeks ($p<0.05$) and 12 weeks ($p<0.01$) (Table VI). There was no statistically significant difference between the Choto-san and placebo groups in the improvement ratings of any subjective symptoms at any of the evaluation points.

Table VI Global improvement rating in a double-blind study.

	4 weeks	8 weeks	12 weeks
Patients number at each evaluation point			
Choto-san	56	55	55
Placebo	64	63	64
Global improvement rating			
Choto-san	1:4:22:26:3	3:12:24:13:3	7:14:25:5:4
Placebo	0:1:21:40:2	1:5:21:29:7	1:7:23:21:12
	N.S.	$p<0.01$	$p<0.001$
Global improvement rating of subjective symptoms			
Choto-san	1:6:21:17:5	3:10:21:9:5	3:14:20:7:3
Placebo	0:4:17:25:7	2:4:20:15:12	3:4:25:8:14
	N.S.	$p<0.05$	$p<0.01$
Global improvement rating of neurological symptoms			
Choto-san	1:1:4:32:3	1:1:7:30:2	1:1:11:26:3
Placebo	0:0:6:41:1	0:1:9:35:1	2:0:9:34:2
	N.S.	N.S	N.S.
Global improvement rating of psychiatric symptoms			
Choto-san	1:2:23:25:5	2:8:28:14:3	4:14:19:13:5
Placebo	1:0:16:36:11	1:2:19:22:19	1:4:22:19:18
	$p<0.05$	$p<0.001$	$p<0.001$
Global improvement rating of disturbance in daily living activities			
Choto-san	1:1:7:31:3	1:2:12:25:2	1:5:10:24:2
Placebo	0:0:7:35:4	0:0:11:30:5	0:1:11:25:9
	N.S.	N.S.	$p<0.05$

Values of Choto-san and placebo present the number of patients evaluated as remarkable improvement : moderate improvement : slight improvement : unchanged : aggravation, respectively.
Others were evaluated as no symptom. p value : Mann-Whitney test.

Neurological symptoms : There was no statistical significance between the Choto-san and placebo groups in the global improvement rating of neurological symptoms at any of the evaluation points (Table VI). There was no statistically significant difference between the Choto-san and placebo groups in the improvement ratings of any neurological symptoms at any of the evaluation points.

Psychiatric symptoms : Choto-san was superior to placebo with statistical significance in the global improvement rating of psychiatric symptoms at 4 weeks ($p<0.05$), 8 weeks ($p<0.001$) and 12 weeks ($p<0.001$) (Table VI). Choto-san showed statistically significant superiority to the placebo in the improvement rating of such psychiatric symptoms as spontaneity of conversation at 8 weeks ($p<0.05$), lack of facial expression at 8 weeks ($p<0.05$), decline in simple arithmetic ability at 12 weeks ($p<0.01$), global intellectual ability at 12 weeks ($p<0.05$), nocturnal delirium at 8 weeks ($p<0.05$), sleep disturbance at 8 weeks ($p<0.05$) and 12 weeks ($p<0.001$), and hallucination or delusion at 8 weeks ($p<0.05$) and 12 weeks ($p<0.001$).

Disturbance in daily living activities : Choto-san was superior to placebo with statistical significance in the global improvement rating of disturbance in daily living activities at 12 weeks ($p<0.05$) (Table VI). Choto-san showed statistically significant superiority to the placebo in the improvement rating of putting on and taking off clothes at 8 weeks ($p<0.05$).

HDS-R : There was no statistical significance between Choto-san and the placebo group in the changes of HDS-Rs from the beginning point (Choto-san, 15.3±4.5 ; placebo, 15.1±4.4) at the evaluation points of 4 weeks (16.7±5.9 ; 16.6±4.9), 8 weeks (18.0±6.4 ; 17.3±5.3) and 12 weeks (19.3±6.6 ; 17.4±6.0). The Choto-san group tended to be higher than the placebo group at 12 weeks, but the statistical significance was less than 0.1.

Overall safety rating : There was no statistically significant difference between the Choto-san and placebo groups in terms of overall safety rating. It

Table VII Utility rating in a double-blind study.

	Very useful	Useful	Slightly useful	Useless	Harmful
Choto-san	8	18	18	13	2
Placebo	1	12	20	25	8

$p<0.001$: Mann-Whitney test

was reported that five Choto-san and two placebo cases possibly suffered adverse effects : urticaria, diarrhea, appetite loss, heartburn and hypertension in the Choto-san group, and oral bitterness and liver dysfunction in the placebo group. In all these cases, their complaints disappeared during the course of the trial or after its discontinuation.

Utility rating (Table VII) : Choto-san showed statistically significant superiority ($p<0.001$) to the placebo in the utility rating.

Discussion

Dementia is mainly classified into two types, dementia of the Alzheimer type and vascular dementia. Many efforts have been made for the development of drugs in the treatment of dementia, including cerebral metabolic activators. However, in general, it is recognized that the treatment of dementia is very difficult. The reason for this is that dementia of the Alzheimer type is a degenerative and progressive disease, and vascular dementia also thought to be a naturally progressive disease brought about by the recurrence of cerebrovascular accidents and aging. However, if progression of vascular dementia would stop and any accompanying symptoms would improve, this would be of much benefit to the patients of vascular dementia.

In Japan, the clinical efficacy of Choto-san has been reported for such symptoms as headache, dizziness, [2] vertigo, [2] tinnitus, [1] shoulder stiffness and so on mainly accompanied by cerebrovascular sclerosis, cerebrovascular disorders and hypertension in relatively elderly patients. Furthermore, the effectiveness of Choto-san on dementia of the Alzheimer type has also been reported. [3] First, for the purpose of objectively evaluating the efficacy of Choto-san on vascular dementia and accompanying symptoms, we planned a well-placebo-controlled study of Choto-san.

In the well-controlled study, Choto-san was found to be superior to the placebo with statistical significance in the global improvement rating, utility rating, global improvement rating of subjective symptoms, global improvement rating of psychiatric symptoms and global improvement rating of disturbance of daily living activities. Furthermore, in the Choto-san group, HDS-Rs at all of the evaluation points at 4, 8 and 12 weeks were significantly higher than at the beginning. These results suggest that Choto-san is effective in the treatment of vascular dementia.

However, there may be a bias for evaluation of a drug in a well-controlled study, because investigators know whether the drug is active or not. Therefore, to evaluate the efficacy of Choto-san more objectively, we carried out a double-blind study. In the double-blind study, as with the previous well-controlled study, Choto-san was statistically superior to the placebo in the global improvement rating, utility rating, global improvement rating of subjective symptoms, global improvement rating of psychiatric symptoms and global improvement rating of disturbance of daily living activities.

Choto-san is a Kampo formulation composed of 11 herbs, those are Chotoko (釣藤鉤), Uncariae Uncis Cum Ramulus, *Uncaria rhynchophylla* MIQUEL or *sinensis* OLIVER, Chimpi (陳皮), Aurantii Nobilis Pericarpium, *Citrus unshiu* MARKOVICH, Hange (半夏), Pinelliae Tuber, *Pinellia ternata* BREITENBACH, Bakumondo (麦門冬), Ophiopgonis Tuber, *Ophiopogon japonicus* KER-GAWLER, Bukuryo (茯苓), Hoelen, *Poria cocos* WOLF, Ninjin (人参), Ginseng Radix, *Panax ginseng* C.A. MEYER, Kikka (菊花),Chrysanthemi Flos, *Chrysanthemum morifolium* RAMATULLE or *indicum* LINNÉ, Bofu (防風), Saposhnikoviae Radix, *Saposhnikovia divaricata* SCHISCHKIN, Kanzo (甘草), Glycyrrhizae Radix, *Glycyrrhiza uralensis* FISCHER or *Glycyrrhiza glabra* LINNÉ, Sekko (石膏), Gypsum Fibrosum, $CaSO_4 \cdot 2H_2O$ and Shokyo (生姜), Zingiberis Rhizoma, *Zingiber officinale* ROSCOE.

Among these herbs, Chotoko is recognized as the most important, and its pharmacological function has already been investigated. It was demonstrated that the extract of Chotoko and its fraction possess

hypotensive activity,[9,10] and the principle of Chotoko has the action of a calcium antagonist.[11] Concerning the central nervous system, it was revealed that the alkaloids obtained from Chotoko were partial agonists for 5-HT receptors in rats,[12] and Chotoko extract had an activating effect on the dopaminergic system and an inhibitory effect on lipid peroxidation in iron-induced acute epileptic rats.[13] As to the other herbs comprising Choto-san besides Chotoko, it is known that Ninjin has many effects, such as an activating effect on the central nervous system by brain monoamine-related substances in mice,[14] anti-fatigue effect on exhaustive exercise in mice,[15] anti-thrombic effect in experimental models of disseminated intravascular coagulation in rats,[16] and so on. Furthermore, Kanzo has an anti-platelet action[17] and possible regulation of cellular senescence.[18] In total, then, clinical effects of Choto-san on vascular dementia in this study are thought to be due to these and other unknown effects of the respective herbs that comprise Choto-san. Further pharmacological investigations on the efficacy of Choto-san are anticipated.

From the results of the present well-controlled and double-blind studies, it was suggested that Choto-san has a favorable effect on vascular dementia and can be recommended as treatment for this condition.

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