

## Therapeutic effect of Sino-Japanese (Kampoh) medicine on rheumatoid arthritis

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### Abstract

The effect of traditional Sino-Japanese (Kampoh) medicine on rheumatoid arthritis (RA) was investigated clinically. In 95 cases RA Kampoh medicine was markedly effective in 27 % and effective in 41 % of the cases. Kampoh formulations, Keisi-syakuyaku-timo-tô (KST), Keisi-ka-ryô-zyutubu-tô (KRT) and Keisi-ni-eppi-ittô (KET) were frequently applied in this order, according to the Kampoh diagnostic criteria. Among these cases, withdrawal of steroid agents, D-penicillamine and gold preparations was successfully achieved. These results indicate that complementary usage of Kampoh medicine has a certain role on the therapy of RA.

**Keywords** rheumatoid arthritis, Kampoh medicine, traditional Chinese medicine, Cinnamoni Cortex, Paeoniae Radix, Glycyrrhizae Radix, Zingiberis Rhizoma

**Abbreviations** A.R.A. ; American rheumatism association, RA ; rheumatoid arthritis, KET ; Keisi-ni-eppi-ittô (Gui-Zhi-Er-Yue-Bi-Yi-Tang) ; 桂枝二越婢一湯, KRT ; Keisi-ka-ryô-zyutubu-tô (Gui-Zhi-Jia-Ling-Shu-Fu-Tang) ; 桂枝加苓朮附湯, KST ; Keisi-syakuyaku-timo-tô (Gui-Zhi-Shao-Yao-Chih-Mu-Tang) ; 桂枝芍藥知母湯

### Introduction

Though rapid progress has been made in the analysis of pathogenesis of rheumatoid arthritis (RA), its cause still remains unclear. Modern Western medicine which is mainly based on etiological treatment has been faced with difficulty concerning the therapy of systemic disease such as RA.

On the other hand, therapy of traditional Sino-Japanese (Kampoh) medicine<sup>1)</sup> can be done regardless of diagnosis or cause as in modern Western medicine. Since extract forms of Kampoh medicine were devised, Kampoh formulations have been widely used for RA in our country for the past 10 years. However only a few

reports<sup>2-4)</sup> can be subjected to modern medical evaluation in terms of diagnostic standards and parameters of efficacy evaluation.

The present study was undertaken in an attempt to clarify the significance of Kampoh medicine for RA therapy in relation to modern Western medicine.

### Materials and Methods

Under the criteria of the American Rheumatism Association (A.R.A.),<sup>5)</sup> a total of 95 cases (63 of classical RA and 32 of definite RA) were investigated. The sex, age and average observation period of the cases are listed in Table I.

According to the A.R.A. anatomic stages,<sup>6)</sup> the subjects comprised 14, 29, 22 and 30 cases for

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stage I, II, III and IV, respectively. The overall functional capacity is estimated by the A.R.A. functional class.<sup>6)</sup>

Efficacy evaluation was made by means of

the Lansbury's index<sup>6)</sup> consisting of four items : duration of morning stiffness, grip strength, joint count and erythrocyte sedimentation rate. In order to evaluate the efficacy of treatment in

Table I Descriptive statistics of 95 RA patients.

	male	female	total
number of cases	18	77	95
average age	52.9±14.5	49.3±10.4	50.0±11.3
average contraction period (years)	6.0± 5.8	7.2± 6.9	7.0± 6.7
average observation period (months)	24.5±10.1	23.2± 9.4	23.4± 9.5
mean±SD			

Table II The herbs comprising Kampoh formulations used in this study.

Keisi-syakuyaku-timo-tô (KST)

Atractylodis Rhizoma	5.0 gram	from China*
Cinnamomi Cortex	4.0	China*
Anemarrhenae Rhizoma	4.0	China*
Ledebouriellae Radix	4.0	China*
Paeoniae Radix	3.0	Japan*
Ephedrae Herba	3.0	China*
Glycyrrhizae Radix	2.0	China*
Zingiberis Rhizoma	1.0	China*
Aconiti Tuber	1.0 - 4.0	Japan**

Keisi-ka-ryô-zyutubu-tô (KRT)

Zizyphi Fructus	4.5 gram	from China*
Hoelen	4.5	North Korea*
Cinnamomi Cortex	4.5	China*
Paeoniae Radix	4.5	Japan*
Glycyrrhizae Radix	3.0	China*
Zinziberis Rhizoma	1.0	China*
Atractylodis Rhizoma	5.0	China*
Aconiti Tuber	1.0 - 4.0	Japan**

Keisi-ni-eppi-ittô (KET)

Gypsum Fibrosum	5.0 - 10.0 gram	from China*
Ephedra Herba	3.0	China*
Cinnamomi Cortex	3.0	China*
Zizyphi Fructus	4.0	China*
Paeoniae Radix	3.0	Japan*
Glycyrrhizae Radix	3.0	China*
Zingiberis Rhizoma	1.0	China*

Note: Each drug was mixed with 600 ml of water and boiled to 300 ml. The decoction was administered 3 times a day before meals.

\*Supplied by Tochimoto-Tenkaidô Co., Ltd. Osaka

\*\*Supplied by Uchida Wakan-Yaku Co., Ltd. Tokyo

cases of active and inactive RA, the following criteria were made in this study : in active RA, 40 % or more improvement of the index was regarded as marked effect, 20 % or more improvement as effect, 10 % or worsening to a greater degree as aggravation, and others as no alteration. Active RA consists of at least three of the following requirements : (1) pain on exercise or tenderness in 6 or more joints, (2) at least three swollen joints, (3) duration of morning stiffness 45 minutes or more, (4) Westergren method for erythrocyte sedimentation rate 28 mm/h or more, and (5) grip strength 130 mmHg or less.

The components of Kampoh formulations used in this study are listed in Table II. The indication of three formulations is as follows : (1) KST is indicative of joint pain in the extremities, emaciation, edema of the feet, vertigo, gasping, and nausea. Destruction of joints, dry skin and anemia are also indicated. Perspiration or thirst is rarely present. (2) KRT is applied in cases such as mild chills (anemophobia), joint pain, slight edema of the feet, difficulty in urination, muscle spasm and perspiration. Thirst and dry skin are signs of contra-indication. (3) KET is prescribed in such cases as joint pain with hot flashes, thirst, perspiration, slight edema and difficulty in urination. Weak pulse and paleness of the face are signs of contra-indication.

## Results

### *Efficacy of the Kampoh treatment*

The results are summarized in Table III. Of 63 RA cases, treatment was markedly effective in 16 cases and effective in 32 cases. On the other hand, of the 26 inactive RA cases it was markedly effective in 9 cases and effective in 7 cases. In total, 68 % of these cases were noted to be effective, and aggravation was noted in only 5 cases (5 %).

### *Changes in the anatomic stages and the functional class*

During the period observed (12-45 months) progress of anatomic stages was found in 7 cases of 77 subjects. Of these cases, the stages changed from III to IV in 2 cases, from II to III in 3 cases and from I to II in one case. In terms of changes in the functional class, improvement by 2 grades was noted in 5 cases of 83 subjects, improvement by one grade in 42 cases. Improvement in overall daily function capacity was noted in a total of 57 %. Aggravation was noted in only one case (Table IV).

### *On the combined Western drugs during the investigation*

At the time of the initial examination, 14 subjects had been under steroid therapy in an

Table III Effect of Kampoh treatment on 95 RA patients.

	Active RA	Non-active RA	Total
markedly effective	16	9	25
effective	32	7	39
no alteration	18	8	26
aggravation	3	2	5
Total	69	26	95

Table IV Changes in functional class following Kampoh treatment.

Improved					no alteration	Aggravation
2 grade		1 grade				
IV to II	III to I	IV to III	III to II	II to I		II to III
1	4	2	30	10	35	1

Table V Adverse effects observed during the period of Kampoh treatment.

	up to 6 months	12 months	18 months	24 months	over 24 months	Total
RBC <sup>a)</sup>	0	2	1	1	3	7
Hb <sup>b)</sup>	0	3	5	1	6	15
S-GOT <sup>c)</sup>	0	0	0	0	0	0
S-GPT <sup>c)</sup>	0	0	0	0	0	0
BUN <sup>d)</sup>	0	0	1	0	2	3
Creatinine <sup>e)</sup>	0	0	0	0	0	0

The following criteria were used for adverse changes :

<sup>a)</sup>Decreased  $50 \times 10^4/\text{mm}^3$  or more.

<sup>b)</sup>Decreased 1.5 g/dl or more.

<sup>c)</sup>Increased 10 Karmen-Uv unit or more.

<sup>d)</sup>Increased 5 mg/dl or more.

<sup>e)</sup>Increased 0.5 mg/dl or more.

other clinic, 11 subjects had been given gold preparations, and 3 subjects had been administered D-penicillamine. Following the treatment with Kampoh medicine, 12, 7, and 3 of the subjects respectively were able to stop using these drugs.

During the period of treatment with Kampoh medicine, 3 subjects used gold preparations (two of them discontinued its use in 3 months), 7 subjects used oral anti-inflammatory agents (5 of them discontinued its use in several months), 32 subjects used suppositories of anti-inflammatory agents. No subjects used either steroids or D-penicillamine agents during the experimental period.

#### *Effective formulations of Kampoh medicine*

Of the formulations of Kampoh medicine, KST (51 %), KRT (32 %) and KET (11 %) were frequently applied in this order. These three formulations accounted for a total 94 % of all the effective formulations. The remaining 6 % of the formulations are Sigyaku-tô (Si-Ni-Tang), Eppika-zyutu-tô (Yue-Bi-Jia-Shu-Tang), Bô-i-ôgi-tô (Fang-Yi-Huang-Qui-Tang) and Yokuinin-tô (Yi-Yi-Ren-Tang).

#### *Evaluation of the safety of Kampoh treatment*

Adverse effects observed during the period of Kampoh treatment were mild pruritus and eruption in 2 cases but these symptoms were easily controlled by reducing the dosage of formulations. Abnormal changes of laboratory data and their onset are listed in Table V. In 7.5 % of the cases, a decrease in red blood cell count by  $50 \times$

$10^4/\text{mm}^3$  or more was noted. A decrease of hemoglobin by 1.5 g/dl or more was noted in 16.1 % of the cases. An increase of serum urea nitrogen levels by 5 mg/dl or more was noted in 3.2 % of the cases. No abnormalities were found in the levels of serum GOT, GPT, LDH and creatinine.

#### *Effects of Kampoh medicines on overall physical condition*

As shown in Fig. 1, weight gain or loss was experienced in almost half of the cases. Appetite, sleep, and fatigue were improved in many cases. It was observed that the sensitivity to colds was reduced and resistance against infection was increased. Improvement of digestion was found in 17 % and aggravation, in about 2 %. Improvement in the warmth of extremities was experienced in about 40 % of the cases, which is considered to be due to improved peripheral circulation.

## Discussion

Several reports<sup>2-4)</sup> have been made on the treatment of RA with Kampoh medicine but there are no other reports in Japan where RA was treated with Kampoh medicine over long periods, as in this report, in terms of objective evaluation standards including the anatomic stages, functional classes and Lansbury's index.

#### *Efficacy of Kampoh medicine*

The subjects had a general distribution in regard to sex ratio, average age, and average length of condition. In this study, anatomic stages

Body weight	increased 25.5 %	not altered 46.8 %	decreased 27.7 %
Appetite	improved 36.2 %	not altered 63.8 %	
Sleep	improved 36.1 %	not altered 59.6 %	*
Fatigue	improved 25.5 %	not altered 59.6 %	* 14.9 %
Sensitivity to colds	improved 48.9 %	not altered 44.7 %	*
Sensitivity to tonsillitis	improved 17.0 %	not altered 78.7 %	*
Gastrointestinal conditions	improved 17.0 %	not altered 80.9 %	*
Coldness of extremities	improved 40.4 %	not altered 53.2 %	*

\* ) aggravated

Fig. 1 Effects of Kampoh medicine on overall physical condition.  
The evaluation was made through questionnaire and progress notes described after one year of treatment.

of the subjects were more advanced than in another reports,<sup>7,8)</sup> which may be related to their medical histories, i.e. most of them had passed through the network of modern medical treatment.

In efficacy evaluation of this investigation, time of fatigue onset and a daily dose of aspirin required to suppress pain using Lansbury's activity indices were excluded because the former is problematic as an item of objective evaluation and the latter, not adequate to the Japanese. Therefore, Lansbury's index was calculated using 4 items in accordance with the method of the Japan Rheumatism Association Efficacy Evaluation Committee.

Significant variations in Lansbury's activity indices are considered to be about 20 %,<sup>6)</sup> and we judged improvement by 20 % or more as effective for active RA. For non-active RA, improvement by 10 % or more was taken as effective in the present study though a question remains in the determination of values of significant variations. Aggravation was taken as worsening by 10 % or more, which is a very strict criterion.

Under the above conditions, efficacy was 76 % for active RA, 62 % for inactive RA, and 68 % in total. The fact that aggravation remained at 5

% should be of significance in consideration of the absence of the use of steroids and D-penicillamine.

#### *Changes in the anatomic stages and the functional class*

Observation for up to 45 months in radiological examination of bone structures revealed progress in 7 of 77 subjects. A little progress in bone changes was noted in a few cases within the same stage. Improvement was observed in one case. For changes in the class, improvement in daily functions was noted in 57 % of 83 subjects. Since each functional class has a considerable grade of variation, improvement by one grade means a great deal of improvement in daily functions.<sup>6)</sup> The results of this study revealed that Kampoh medicine brings more satisfactory results in the functional class of RA than in the anatomic stage.

#### *On the combined Western drugs during the treatment*

As described in a textbook of internal medicine,<sup>9)</sup> steroid agents should not be employed in the management of RA until there has been a sustained trial of more conservative therapy. The results of this study showed that Kampoh medicine was highly possible in withdrawal from ster-

oid therapy. This fact suggests that Kampoh medicine qualifies for one of the conservative therapies which should be conducted prior to steroid therapy.

#### *Effective formulations of Kampoh medicine*

Recently we have reported the anti-inflammatory effects of three effective formulations for RA,<sup>10)</sup> and have reported that the mechanism of these formulations might be accounted for by the immunological reaction and the pathways through chemical mediators. The pharmacological effects of each medicinal plant from which these formulations are composed have also been clarified in recent years. Yagi *et al.*<sup>11)</sup> have reported that Cinnamomi Cortex shows an inhibition of immunological hemolysis, and Arthus reaction through an inhibition of complement system. And Tamura *et al.*<sup>12)</sup> have revealed that glycyrrhizin, which is a main component of licorice, inhibits delta-5-beta-reductase and enhances steroids effects.

#### *Evaluation of safety of the Kampoh treatment*

Treadal *et al.*<sup>13)</sup> have reported the adverse effects of long term treatment with corticosteroids in RA patients, and revealed that severe side-effects in the corticosteroids were bruising (16 %), mooning (10 %), dyspepsia (10 %), severe degree of weight-gain (5 %), edema (5 %), hypertension (5 %), and emotional instability (5 %). Concerning the side-effects of nonsteroidal anti-inflammatory drugs, Maccagno and Santoro<sup>14)</sup> have reported a comparative study of tiaprifenic acid and diclofenac for the treatment of RA, and revealed the frequency of side-effects of these drugs were as follows; Epigastric pain (40 %), diarrhea (13 %), pyrosis (13 %) and enterocolitis (13 %).

However, during the Kampoh treatment, there was no significant adverse effects mentioned above.

Routine examinations for side effects in Kampoh treatment revealed the most marked findings of decreased RBC and hemoglobin content. However, anemia is in close relation with the condition of RA, therefore cannot be considered a side effect caused through the effects of medicinal plants.<sup>15)</sup> Careful observation for a longer

period would be necessary for evaluating this problem. There are few, if any, questions in regard to change in the other examination items, and it may be considered that the treatment is very safe.

#### *Effects of Kampoh medicine on overall physical condition*

The present study has revealed that there were not a few cases where appetite or gastrointestinal condition were improved, and the great advantage of Kampoh treatment is that it can be used to treat RA without causing gastrointestinal complications. As many as half of the cases became more resistant to colds, a favorable condition for patients with RA which is aggravated by infection. This suggests that Kampoh treatment might contribute to the improvement of the immune responses in some manner.<sup>12, 15, 16)</sup>

As discussed above, treatment of RA by Kampoh medicine has shown satisfactory results in both efficacy and safety, and this indicates that Kampoh could be of value when incorporated into the therapeutic program of RA treatment.

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