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ORIGINAL ARTICLE

Hypouricemic effect and regulatory effects on autonomic function of *Shao-Yao Gan-Cao Tang*, a Chinese herbal prescription, in asymptomatic hyperuricemic vegetarians

Tsung-Hsiu Wu · Lih-Chi Chen · Ling-Ling Yang

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Abstract *Shao-yao Gan-Cao Tang* (SYGCT) is a popular Chinese herbal prescription which is composed of Paeoniae Radix and Glycyrrhizae Radix. The uric acid-lowering effects and regulatory effects on autonomic functions of SYGCT in vegetarians with asymptomatic hyperuricemia were evaluated in the present study. All the hyperuricemic vegetarians in experimental group and the normal healthy subjects in control group were administered SYGCT three times daily for 4 weeks. The blood levels of uric acid and general autonomic system function examinations were performed at baseline and after 4-week treatment. The activities of autonomic function were evaluated by a modified method from Wenger's analyses of autonomic variables. After 4-week treatment of SYGCT, a significant reduction of serum uric acid levels was found in the hyperuricemic vegetarians. SYGCT could increase the sympathetic activities of the hyperuricemic vegetarians with deficient-syndrome, but had no significant effects in the excess-syndrome subjects.

Keywords *Shao Yao Gao Cao Tang* · Chinese herbal prescription · Hyperuricemia · Autonomic functions

T.-H. Wu · L.-C. Chen · L.-L. Yang
College of Pharmacy, Taipei Medical University, Taipei, Taiwan

T.-H. Wu
Department of Pharmacy, Hei-Ho Hospital, Nantou, Taiwan

L.-C. Chen (✉)
Department of Pharmacy, Taipei City Hospital, 145, Zheng-zhou Rd, Taipei 103, Taiwan
e-mail: lcchen2007@gmail.com

Introduction

Along with economic development, the number of people suffering high blood uric acid and gout is also on the rise. Statistics reveal that around 5% (2–18%) of people suffer from high blood uric acid while 5–10% suffer from gout. High blood uric acid is related to abnormal purine metabolism. Hyperuricemia is indicative of a high level of uric acid in the blood (>7 mg/dl). Human beings have higher levels of uric acid (hyperuricemia) because of a deficiency of the hepatic enzyme, uricase, and a lower fractional excretion of uric acid. Approximately two-third of total body urate is produced endogenously, while the remaining one-third is from dietary purines. Hyperuricemia may also occur from increased production, or a combination of the two mechanisms. The prevalence rate of asymptomatic hyperuricemia in the general population is estimated at 2–13%. High-purine diets, alcohol consumption, and obesity were the risk factors contributed to of hyperuricemia. It was generally suggested that increased consumption of foods from plant sources (especially fruit and vegetables) reduce the risk of hyperuricemia; however, our clinical observation previously indicated that higher blood uric acid concentrations were found in the Chinese Buddhist vegetarians who usually consumed a fairly large amount of soy products as protein sources.

Shao-Yao Gan-Cao Tang (SYGCT), a traditional Chinese herbal prescription, was sourced from the Chinese Medical Classics text—*Shanghan lun* in 210 CE. The book *Prescriptions of Traditional Chinese Herb Medicines* indicated the prescription could "*healing the abdominal pain by keeping the equilibrium in the stomach*". SYGCT, composed of Paeoniae Radix and Glycyrrhizae Radix in an even dose, is the popular Chinese prescription and is widely used in China and Japan for acute abdominal pain and

muscles stiffness. The Paeoniae Radix can scatter the *liver*, and Glycyrrhizae Radix can postpone the *liver* and equilibrate the *spleen*. Therefore the herbal formula is categorized into a standard prescription with *equilibrium* functions, capable of healing deficient-syndrome with internal fever [1].

Hyperuricemia has been a significant metabolic disorder for the Chinese people in Taiwan. Especially, it is interesting that higher blood uric acid concentrations were found in the Chinese Buddhist vegetarians. SYGCT, one of the traditional Chinese medicines with bi-directional regulatory effects, is widely used for the management of various chronic diseases; however, there is no data associated with its effectiveness for the hyperuricemic population. Therefore, the present case-control study was conducted to explore the hypouricemic effect and regulatory effects on autonomic function of SYGCT in Buddhist vegetarians with asymptomatic hyperuricemia.

Materials and methods

Subjects

The study subjects in experimental group were male Buddhist vegetarians with asymptomatic hyperuricemia enrolled at Fu Yuan Buddhist College, Taipei, Taiwan. Subjects in control group were normal, non-vegetarian healthy males without treatments. Observations were made from April to June 2005. The inclusion criteria for hyperuricemic subjects were that blood uric acid level was greater than 7.0 mg/dl. Subjects with severe metabolic problems, renal impairment, gout or arthritis were excluded. General medical examinations and physical constitution diagnosis for the subjects in the experimental group were performed by a medical doctor. Based on the physical constitution in Chinese medicine, the experimental subjects were categorized into an excess-syndrome group and a deficient-syndrome group. No therapeutic drugs had been given within the last 2-month period. Informed consents were obtained from all subjects after being given a full explanation of the study.

Preparation of the Chinese prescriptions

SYGCT, which is composed of Paeoniae Radix and Glycyrrhizae Radix (1:1, w/w), was prepared from the roots of *Paeonia lactiflora* and *Glycyrrhiza uralensis*. All the Chinese herbal materials were purchased from the Shunyuan herbal Pharmacy, Taipei and authenticated in Taipei Medical University. The prescriptions were prepared according to Chinese original documents. The raw herb materials, weighing with a daily quantity, were extracted twice by refluxing with the boiling water (1:20, w/v) for 1 h. The decoction was filtered and then concentrated to 270 ml, which is equivalent to a daily dose (90 ml three times a day).

Drug treatment and evaluation

The hyperuricemic vegetarians in experimental group, including excess- and deficient-syndrome groups, were administered SYGCT with the dose of 90 ml three times daily for 4 weeks. Normal healthy subjects in control group were given the same dose of SYGCT. The blood levels of uric acid and general autonomic system function examinations were performed at baseline and after 4-week treatment. For the blood uric acid test, 10–15 ml of blood was collected after overnight fasting, and a Hitachi 7060 analyzer was performed for the analysis. Any possible signs of adverse effect during the study period reported from the patient were monitored by a series of physical examinations.

Physical constitution diagnosis

Based on the theory of Chinese medicine, the physical constitution is divided into two classifications by pulse. All subjects were examined by an assigned Chinese medical doctor. Excess-syndrome subjects are *wet*, *hot*, and internally blocked. Excessively *hot* persons are normally *bigger*, ruddy, boisterous, do not like heat but like cold drinks, easily get dehydrated in summer, and constipated, and have high blood pressure when faced with difficult situations, and have headaches—symptoms of sympathetic reactions. Deficient-syndrome subjects have *spleen*, *kidney*, and *liver* deficiencies. They are usually thin, pale or yellowish, soft spoken, cannot stand cold, like to take hot drinks, have numb extremities during the winter, are easily diarrheic when faced with difficult situations, and get stomachaches—symptoms of parasympathetic excitation [2, 3].

Autonomic function assessment

The autonomic function was assessed with the Wenger's analyses of autonomic variables [4] modified by Liang's [5]. The Wenger's regression equation is $y = -28 - 0.194\,X_1 + 0.031\,X_2 + 0.025\,X_3 - 0.792\,X_4 - 0.131\,X_5 + 0.649\,X_6$. In the equation, X_1 is the salivary amount (ml) secreted in 3 min, X_2 is the seated systolic pressure (mmHg), X_3 is the seated diastolic pressure (mmHg), X_4 is the mean time of the pulse interval (s), X_5 is the mean time of the respiratory interval (s), and X_6 is the hypoglossal body temperature (°C). The variables are entered into the equation to obtain the equilibrium index (y value). The equilibrium index $y = 0 \pm 0.56$ means a normal value;

$y > +0.56$ is abnormal which shows increased sympathetic functions; and $y < -0.56$ is abnormal showing decreased sympathetic functions (or increased parasympathetic functions). Subjects undergoing the tests have to sit calmly for 30 min before tests. They should not have high blood pressure, an irregular heart pattern, be feverish, or suffering from extreme blood loss.

Statistics

All data were expressed as means ± SE. The blood levels of uric acid, the values of Wenger's autonomic variables were compared using the paired *t* test for the evolution within group and unpaired Student's *t* test for independent subjects was applied for the comparison between groups. The differences were considered to be statistically significant when $P < 0.05$.

Results

Subjects' general characteristics

A total of 16 normal healthy subjects in the control group and 17 hyperuricemic vegetarians in the experimental group were included in the final analysis. Except for the baseline of blood uric acid level, there was no significant difference in the subjects' general characteristics between the groups. According to the physical constitution diagnosis, the experimental group was divided into an excess-syndrome group (5 subjects) and a deficient-syndrome group (12 subjects). For the safety assessment, no signs of clinical adverse effect were reported during 4 weeks of study period.

Uric acid-lowering effects of SYGCT

The baseline of blood uric acid levels in the experimental group averaged 8.56 ± 0.24 mg/dl. After 4-week treatment of SYGCT, the level dropped to 6.90 ± 0.22 mg/dl with a significant improvement (Table 1). SYGCT showed significant uric acid-lowering effects in the hyperuricemic vegetarians. In the control group, however, no obvious effects were found in the normal healthy subjects.

Autonomic function in hyperuricemic vegetarians

The autonomic function of each study subject was assessed with the Wenger's autonomic variables. Compared with the baseline of Wenger's autonomic variables in the control group, a significantly increased equilibrium index (*y* value) was found in excess-syndrome hyperuricemic vegetarians ($P < 0.05$) and a remarkably decreased equilibrium index ($P < 0.01$) was found in deficient-syndrome subjects. In comparison between excess- and deficient-syndrome groups, there were significant differences in equilibrium index ($P < 0.01$) and autonomic variables ($P < 0.05$) including saliva amount, systolic pressure, diastolic pressure and respiratory interval (Table 2). These results indicated that the subjects in the excess-syndrome group exhibited increased sympathetic activities and the decreased sympathetic activities (or strengthened parasympathetic activities) were shown in the deficient-syndrome subjects.

Regulatory effects on autonomic function of SYGCT

After 4-week treatment of SYGCT, there were no significant alterations in all autonomic variables and equilibrium index within the excess-syndrome group. Regarding to the deficient-syndrome group; however, the significant increase in systolic-, diastolic pressure ($P < 0.05$) and equilibrium index ($P < 0.01$) were found (Table 3). These results showed that SYGCT could increase the sympathetic activities and exhibit a regulatory effect on the autonomic function in the hyperuricemic vegetarians with deficient-syndrome, but had no significant effects in the excess-syndrome subjects.

Discussion

Currently, it is believed that hyperuricemia is related to metabolic disorders such as obesity, high blood pressure, high blood triglycerides, diabetes, and cerebrovascular diseases [6]. Gout is the main clinical manifestation of hyperuricemia and 5–12% of hyperuricemic patients ultimately exhibit the condition. Although hyperuricemia predisposes patients to both gout and nephrolithiasis, therapy is generally

Table 1 Changes in blood uric acid levels within each group

	Control group ($N = 16$)		Experimental group ($N = 17$)	
	Baseline	After 4-week treatment	Baseline	After 4-week treatment
Uric acid levels (mg/dl)	6.04 ± 0.15	5.74 ± 0.22	8.56 ± 0.24	6.90 ± 0.22*

Control group: normal healthy subjects; experimental group: hyperuricemic vegetarians. Values are presented as mean ± SE

* $P < 0.01$ by paired Student's *t* test versus baseline

Table 2 Baseline of autonomic variables

	Control group ($N = 16$)	Experimental group ($N = 17$)	
		Excess-syndrome group ($N = 5$)	Deficient-syndrome group ($N = 12$)
Salivary secretion amount (ml)	0.81 ± 0.08	0.64 ± 0.18	1.14 ± 0.13*+
Systolic pressure (mmHg)	106.44 ± 1.96	111.60 ± 2.14	102.67 ± 2.25+
Diastolic pressure (mmHg)	72.63 ± 1.83	74.60 ± 2.04	68.17 ± 1.66+
Pulse interval (s)	0.91 ± 0.02	0.85 ± 0.06	1.00 ± 0.05
Respiration interval (s)	4.6 ± 0.45	4.12 ± 0.29	5.62 ± 0.41+
Hypoglossal temperature (°C)	36.74 ± 0.09	37.20 ± 0.30	36.81 ± 0.09
Equilibrium index (y)	−0.51 ± 0.09	+0.13 ± 0.28*	−0.98 ± 0.09**++

Control group: normal healthy subjects; experimental group: hyperuricemic vegetarians. Values are presented as mean ± SE

* $P < 0.05$, ** $P < 0.01$ compared with the control group by unpaired Student's t test

+ $P < 0.05$, ++ $P < 0.01$ comparison between excess- and deficient-syndrome groups

Table 3 Changes in autonomic variables within each experimental group

	Excess-syndrome group ($N = 5$)		Deficient-syndrome group ($N = 12$)	
	Baseline	After 4-week treatment	Baseline	After 4-week treatment
Salivary secretion amount (ml)	0.64 ± 0.18	0.88 ± 0.17	1.14 ± 0.13	1.09 ± 0.13
Systolic pressure (mmHg)	111.60 ± 2.14	114.00 ± 2.45	102.67 ± 2.25	111.25 ± 2.76*
Diastolic pressure (mmHg)	74.60 ± 2.04	73.00 ± 2.00	68.17 ± 1.66	74.58 ± 1.68*
Pulse interval (s)	0.85 ± 0.06	0.82 ± 0.06	1.00 ± 0.05	0.95 ± 0.04
Respiration interval (s)	4.12 ± 0.29	4.54 ± 0.40	5.62 ± 0.41	4.82 ± 0.26
Hypoglossal temperature (°C)	37.20 ± 0.30	37.18 ± 0.28	36.81 ± 0.09	36.89 ± 0.11
Equilibrium index (y)	+0.13 ± 0.28	+0.07 ± 0.22	−0.98 ± 0.09	−0.35 ± 0.08**

Values are presented as mean ± SE

* $P < 0.05$, ** $P < 0.01$ comparison within group by paired Student's t test

not warranted in the asymptomatic patients. Recognizing asymptomatic hyperuricemia provides the physician with an opportunity to modify or correct underlying acquired causes of hyperuricemia. Excess production and decreased excretion of uric acid contribute to hyperuricemia, therefore, two types of hypouricemic drugs are commonly used in the management of symptomatic hyperuricemia. Uricosuric drugs reduce the serum urate concentration by increasing the renal excretion of uric acid, and xanthine oxidase inhibitors decrease serum uric acid by inhibiting uric acid synthesis. The uricosuric drugs probenecid and sulfinpyrazone are the most logical hypouricemic agents for underexcretors of uric acid. The uric acid synthesis inhibitor allopurinol is the drug of choice for overproduction of uric acid. Since allopurinol is also efficacious for patients who are underexcretors, it is prescribed most commonly for the management of hyperuricemia. Although allopurinol generally is well tolerated, the frequency of adverse effect increases in the presence of renal insufficiency. The most common adverse effects include gastrointestinal intolerance, bone marrow suppression, renal or hepatic toxicities, and skin rash. Stevens–Johnson syndrome associated with allopurinol is uncommon but has to be noted. Probenecid and sulfinpyrazone also have common adverse effects as gastrointestinal disturbances. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the treatment of choice for acute attacks of gout in most patients. Due to the common and significant adverse effects, NSAIDs should be used sparingly in elderly patients and should be avoided in patients with renal disease and peptic ulcer disease, and in those receiving concurrent systemic anticoagulation. Because of the frequent and potentially dangerous adverse effects associated with these drugs, interest in alternative use of Chinese medicines for managing hyperuricemia is on the rise during these years.

In the present results, SYGCT showed significant uric acid-lowering effects in the hyperuricemic vegetarians but had no obvious effects in the normal healthy subjects. SYGCT may work by way of integrating the actions of each individual herb, as most Chinese herbal prescriptions

do. Traditionally, the Chinese herbal therapy was to alleviate pain and symptoms, improve blood flow and slow disease progression, correct imbalance and adjust immune system, and most importantly, to restore function, boost energy and strong body for better health and quality of life. The use of Chinese herbal medicine is not to take the place of necessary orthodox medical treatment. Combination of the both might be a better choice. While the possibility of uric acid-lowering effect of SYGCT has been raised in this trial, the mechanism and therapeutic role underlying the clinical efficacy deserve further study.

In view of Chinese medicine, hyperuricemia might be caused by *kidney Yin* deficiency, lack of strength in the *spleen*, lack of vital energy in the *kidney*, and dampness and obstruction in the internal condition. In this study, the hyperuricemic vegetarians were divided into excess-syndrome and deficient-syndrome subjects based on the theory of Chinese medicine. Excess-syndrome patients belong to *wet*, *hot*, and obstruction in internal conditions while deficient-syndrome patients have poor spleen, kidney or liver functions. While clinical findings commonly show a mixture of both. The present study demonstrated that, compared with the baseline of Wenger's autonomic variables in the control group, a significantly increased equilibrium index (y value) was found in excess-syndrome hyperuricemic vegetarians and a remarkably decreased equilibrium index was found in deficient-syndrome subjects. In comparison between excess- and deficient-syndrome groups, there were significant differences in equilibrium index and autonomic variables including saliva amount, systolic pressure, diastolic pressure and respiratory interval. It indicated that the subjects in the excess-syndrome group exhibited increased sympathetic activities and the deficient-syndrome subjects exhibited decreased sympathetic activities (or strengthened parasympathetic activities). These findings proved that the physical constitution of excess- and deficient-syndromes could reflect, to a certain degree, sympathetic and adrenal activities.

Regarding to the effects of SYGCT on the autonomic function, after 4 weeks of treatment, there were no significant alterations in all autonomic variables and equilibrium index in the excess-syndrome hyperuricemic vegetarians. It is interesting that; however, the significant increase in systolic-, diastolic pressure and equilibrium index were found in the deficient-syndrome groups. While the deficient-syndrome subjects exhibited decreased sympathetic activities, it indicated that SYGCT could increase the sympathetic activities of deficient-syndrome subjects. These results showed that SYGCT exhibited regulatory effects on the autonomic function in the hyperuricemic vegetarians with deficient-syndrome, but had no significant effects in the excess-syndrome subjects. In accordance with the above disclosures and the previous reports underlying the bi-directional effects of Chinese medicines on the autonomic system [7–14], further studies to explore the mechanism should be in progress.

In conclusion, SYGCT showed significant uric acid-lowering effects in the hyperuricemic vegetarians but had no obvious effects in the normal healthy subjects. While the hyperuricemic vegetarians with the excess-syndrome exhibited increased sympathetic activities and the deficient-syndrome subjects exhibited decreased sympathetic activities. SYGCT could increase the sympathetic activities of deficient-syndrome subjects. It demonstrated that SYGCT exhibited regulatory effects on the autonomic function in the hyperuricemic vegetarians with deficient-syndrome, but had no significant effects in the excess-syndrome subjects.

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