漢方診断学部門　　Department of Kampo Diagnostics

客員教授	柴原　直利	Professor	Naotoshi Shibahara (M.D., Ph.D.)
客員助教授	後藤　博三	Associate Professor	Hirozo Goto (M.D., Ph.D.)
客員助教授	酒井　伸也	Associate Professor	Shinya Sakai (M.D., Ph.D.)
寄付研究部門教員	中川　孝子	Instructor	Takako Nakagawa (Ph.D.)
機関研究員(COE)	郇　明明	Postdoctral Fellow	Huan Mingming (Ph.D.)

◇研究目的

医療保険の薬価に収載されている漢方製剤は147種であり，また生薬は約200種である。平成９年，薬価収載の漢方製剤（いわゆるエキス剤）の全てについて「漢方医学的な病態（証）に基づいて適正に使用すること」が明記された。
証を決定できるようになるためには，基礎概念の学習とともに臨床に根ざした研修を必要とする。にもかかわらず，わが国において体系的にこれを教育する場は，医学部にも薬学部にも未だに整備されていない。
当部門は平成11年４月１日付けで，株式会社ツムラの寄付部門として設置され，本学医学部和漢診療学講座の協力の下に，全国の医師・薬剤師・医薬学生に対して，短期および長期研修コースを提供している。
漢方医学研修カリキュラムを作成するには，古典の学習にとどまらず，証をより客観的なものに育てていく必要がある。
我々は漢方方剤，生薬の薬理作用の研究および漢方医学的病態の解明を学内外諸機関と協力して行っている。

◇研究概要

Ⅰ）　漢方医学的病態からみた漢方方剤の薬理効果の基礎的・臨床的研究

1) 各種漢方方剤の指標物質測定法の開発，及びヒトにおける体内薬物動態の解析
2) 無症候性脳血管障害に対する桂枝茯苓丸の短期および長期効果の検討
3) 生活習慣病に対する桂枝茯苓丸長期投与の効果の検討
4) 動物モデルを用いた微小循環障害に対する漢方方剤の効果の検討
5) 動物モデルを用いた糖尿病性腎症に対する桂枝茯苓丸の長期効果の検討
6) 動物モデルを用いた褥瘡に対する帰耆建中湯の効果の検討

Ⅱ）　病態や証を客観化するための指標を探索する基礎的・臨床的研究

1) 漢方医学的病態の自律神経系検査法による解析
2) 漢方医学的病態の品質工学的手法による解析
3) プロテオミクス解析を用いた鍼灸治療効果の客観的評価法の確立

Ⅲ）　漢方医学的病態の古典的解釈と客観的評価を統合した臨床研修プログラムの開発

1) 漢方医学研修による教育効果に関する検討
2) 傷寒論，金匱要略を中心とする古典の解釈に関する検討

◇著書

1) 後藤博三，寺澤捷年：漢方医学の基礎　漢方医学の特徴について概説できる.「スタンダード薬学シリーズ３　日本薬学会編　化学系薬学　III.自然が生み出す薬物」　市川厚他編，204-207，東京化学同人，東京，2005.
2) 後藤博三，寺澤捷年：漢方医学の基礎　漢方医学の特徴について概説できる.「スタンダード薬学シリーズ３　日本薬学会編　化学系薬学　III.自然が生み出す薬物」　市川厚他編，215-219，東京化学同人，東京，2005.
3) 柴原直利，済木育夫：漢方処方の応用　外科，リウマチ・自己免疫疾患.「スタンダード薬学シリーズ３　日本薬学会編　化学系薬学　III.自然が生み出す薬物」　市川　厚他編，259-262，東京化学同人，東京，2005.
4) 後藤博三，中川孝子：Metabolic Modulators インスリン作用改善薬 -漢方薬-.「内分泌・糖尿病科」，55-61，科学評論社，東京，2005.
5) 後藤博三，寺澤捷年：漢方薬.「治療薬 Up-to-Date2005」，811-820，メディカルレビュー社，東京，2005.
6) 柴原直利，矢野耕也：漢方問診データの MT システムによる定量化の研究と多階 MMTA 法.「品質工学応用講座　コンピュータによる情報設計の技術開発　-シミュレーションと MT システム-」　矢野　宏他編，353-368，財団法人　日本規格協会，東京，2004.（前回未掲載）

◇原著論文

1) **Imanishi N., Andoh T., Sakai S., Satoh M., Katada Y., Ueda K., Terasawa K. and Ochiai H.: Induction of inducible nitric oxide (NO) synthase mRNA and NO production in macrophages infected with influenza A/PR/8 virus and stimulated with its ether-split product. *Microbiol. Immunol.*, 49: 41-48, 2005.**

Abstract: We investigated the inductive activity of infective influenza A/PR/8/34 (PR8) virus and its ether-split product (ESP) on the expression of inducible nitric oxide (NO) synthase (iNOS) and NO production in RAW264.7 (RAW) cells, a murine macrophage (M psi) cell line, and thioglycolate-elicited peritoneal M psi (TPM). In both cells, PR8 virus infection induced iNOS mRNA between 4 hr and 24 hr, attaining a peak value at 12 hr. In correlation with induction of iNOS mRNA, NO amounts increased significantly from 12 to 24 hr. Moreover, this study demonstrated that ESP with the same hemagglutination titer as PR8 virus could induce iNOS mRNA and NO production, although the inductive activity of ESP was weaker than that of PR8 virus. Considering the dual role (beneficial and detrimental roles) of NO on certain inflammatory disorders and virus infections, the inductive activity of influenza virus on the iNOS-mediated NO production independent of its infectivity might contribute to a modification of influenza virus infection.

2) **Kogure T., Ltoh K., Tatsumi T., Sekiya N., Sakai S., Shimada Y., Tamura J., and Terasawa K.: The effect of Juzen-taiho-to/TJ-48 on the expression of killer-cell immunoglobulin-like receptors (CD158a/b) on peripheral lymphocytes in vitro experiment. *Phytomedicine*, 12: 327-332, 2005.**

Abstract: Juzen-taiho-to (TJ-48), a mixture of extracts from 10 medicinal herbs, has been used traditionally to treat patients with anemia, anorexia or fatigue. It is well known that the treatment of TJ-48 result in the decrease of patient's complaints, as well as the increase of NK cytolytic activity (NK activity) although its augmentation is not clear in the other kampo formula from the clinical viewpoint. To investigate its biological activities, such as the augmentation of NK activity, we analyzed the effects of

TJ-48 on the expression of killer-cell immunoglobulin-like receptors (KIRs) in vitro experiment. The peripheral lymphocytes were incubated in medium alone, or medium containing TJ-48 or interleukin-2 (IL-2) plus TJ-48 at several concentrations for 48 h. After each incubation, cells were collected and their KIRs were detected by flow cytometry using monoclonal antibodies CD158a and CD158b. TJ-48 increased the populations of CD16+CD158a+ and CD16+CD158b+ cells in a dose-dependent manner. In contrast, CD16-CD158a/b+ cells did not increase. Additionally, the extract of TJ-48 enhanced the increase of KIRs expression induced by IL-2. These actions contribute to the augmentation of NK cytolytic activity by TJ-48, and might explain, in part, its antitumor effect which has been observed in vivo.

3) **Takagi S., Goto H., Shimada Y., Nakagomi K., Sadakae Y., Hatanaka Y., and Terasawa K.: Vasodilative effect of perillaldehide on isolated rat aorta. *Phytomedicine*, 12: 333-337, 2005.**

Abstract: The vasodilative effect of perillaldehyde, one of the major oil components in Perilla frutescens BRITTON, was studied using isolated rat aorta. Perillaldehyde at final concentrations of 0.01 to 1 mM showed dose-dependent relaxation of the aorta contracted by treatment with prostaglandin F2alpha or norepinephrine. Neither the presence of NG-nitro-L-arginine methyl ester nor removal of the aortic endothelium affected the vasodilatation, suggesting that perillaldehyde exerts a direct effect on vascular smooth muscle cells. The vasodilative effect of perillaldehyde was not inhibited by pretreatment with a beta-adrenergic receptor blocker (propranolol), an inhibitor of phosphodiesterase (theophylline), a delayed rectifier K^+ channel blocker (tetraethylammonium chloride), or an ATP-sensitive K^+ channel blocker (glibenclamide). However, perillaldehyde showed contrasting effects on vasodilatation of the aorta contracted by an influx of extracellular Ca^{2+} - perillaldehyde caused little vasodilatation on the aorta contracted by the Ca^{2+} ionophore A23187, while it inhibited the vasoconstriction induced by treatment with high-concentration K+, which dominantly opened the voltage-dependent Ca^{2+} channel. These results suggest that the vasodilative effect of perillaldehyde is derived from blocking the Ca^{2+} channels.

4) **Satoh N., Sakai S., Kogure T., Tahara E., Origasa H., Shimada Y., Kohoda K., Okubo T., and Terasawa K.: A randomized double blind placebo-controlled clinical trial of Hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness N of one and responder restricted design. *Phytomedicine*, 12: 549-554, 2005.**

Abstract: OBJECTIVE: To evaluate the effects of Hochuekkito, a traditional Japanese and Chinese medicine, in the treatment of elderly patients with general weakness. To devise a suitable study design for assessing the clinical effectiveness of traditional herbal medicines. METHODS: Fifteen elderly patients (mean +/- SD: age 78.4 +/- 7.8; m/f 3/12) participated in this study. A multicenter, prospective, randomized, double-blind, placebo-controlled study with N of one and responder restricted design was performed. After the run-in period, the patients were divided into responders and non-responders. Only responders were entered in the study, and were randomized into three groups: an active-placebo group, a placebo-active group and an active-active group. The study consisted of two 6-week terms with a 2-week washout period in between. We assessed the Short Form 36 Health Survey (SF-36) and Profile of Mood States (POMS) as an endpoint of quality of life (QOL). In addition, we assessed the biodefense status by measuring the natural killer cytolytic activity (NK activity), IL-2 producing activity of peripheral lymphocytes, lymphocyte proliferating activity and lymphocyte cell-surface antigens. RESULTS: The physical component summary of the SF-36 analysis significantly improved in the Hochuekkito-treated group. Four components (A-H: anger-hostility, F: fatigue, T-A: tension-anxiety, C: confusion) out of six improved in the Hochuekkito-treated group in the POMS analysis. Lymphocyte proliferating activity improved in the Hochuekkito-treated group but not significantly. Concerning the surface antigens of peripheral lymphocytes, the population of CD3 positive cells and CD3CD4 double positive cells increased in the Hochuekkito-treated group. CONCLUSION: We revealed that Hochuekkito improved

the QOL and immunological status of elderly patients with weakness by randomized controlled trial. Our study design might be useful for assessing the efficacy of traditional herbal medicine in the future.

5) **Sekiya N., Shimada Y., Shintani T., Tahara E., Kouta K., Shibahara N., and Terasawa K.: Reduction of perception of chronic fatigue in an observational study of patients receiving 12 weeks of kampo therapy. *J. Altern. Complement. Med.*, 11: 895-901, 2005.**

Abstract: Objective: The aim of this study was to observe the influence of Kampo therapy on latent chronic fatigue of patients with chronic diseases. Subjects: One hundred and seventy-three (173) consecutive patients with chronic diseases came to our department for the first time. Design: This was a prospective study. Patients were divided into two groups: a chronic fatigue group (CFG) and a nonchronic fatigue group (NCFG). Based on Kampo diagnosis, both groups were prescribed Kampo formulae as an extract or decoction for 12 weeks. Outcome Measures: By using questionnaires, patients were assessed concerning their physical and mental types of fatigue, their sleep situation, and their attitude toward work or housekeeping, both before and after 12 weeks of treatment, according to Kampo diagnosis. Results: The mental fatigue, physical fatigue, and sleep scores of both groups, and the work score of CFG, were decreased. The rate of reduction of the fatigue score was significantly greater in CFG than in NCFG. The factor responsible for this difference in fatigue score was physical fatigue. Conclusions: A reduction of the perception of chronic fatigue was observed in patients receiving 12 weeks of Kampo therapy.

6) **Nakagawa T., Yokozawa T., Kim H.J., and Shibahara N.: Protective effects of gamma-aminobutyric acid in rats with streptozotocin-induced diabetes. *J. Nutr. Sci. Vitaminol.*, 51: 278-282, 2005.**

Abstract: The effects of gamma-aminobutyric acid (GABA) in rats with experimental diabetes mellitus were examined. Diabetes mellitus was induced in adult male Wistar rats by streptozotocin (STZ) injection. Oral administration of GABA (100 or 200 mg/kg body weight/d) for 10 d to the diabetic rats resulted in a significant decrease in their serum glucose level. GABA also reduced the level of glycosylated protein in serum, indicating an improvement of hyperglycemic conditions. Rats with STZ-induced diabetes showed arrested body weight gain and an increase in both liver and kidney weight, whereas oral administration of GABA attenuated the organ hypertrophy induced by hyperglycemia. In addition, the degree of serum thiobarbituric acid (TBA)-reactive substance level was significantly lower in the rats treated with 100 mg GABA, and the degree of TBA-reactive substance in the liver and kidney was reduced by GABA in a dose-dependent manner. These results suggest that GABA treatment protects against the development of diabetic complications resulting from impaired glucose metabolism and enhanced oxidative stress.

7) **Nakagawa T., Yokozawa T., Satoh A., and Kim H.Y.: Attenuation of renal ischemia-reperfusion injury by proanthocyanidin-rich extract from grape seeds. *J. Nutr. Sci. Vitaminol.*, 51: 283-286, 2005.**

Abstract: The effects of proanthocyanidin-rich extract in rats subjected to renal ischemia-reperfusion were examined. Proanthocyanidin-rich extract, which is prepared from grape seeds (Vitis vinifera L.), was given orally at doses of 5 and 10 mg/kg body weight/d for 20 consecutive days prior to ischemia-reperfusion. Administration of proanthocyanidin-rich extract attenuated renal dysfunction, as indicated by serum urea nitrogen and creatinine levels. Additionally, in the ischemic-reperfused kidneys, increased levels of thiobarbituric acid (TBA)-reactive substance and alterations of antioxidant enzyme activities such as superoxide dismutase, catalase and glutathione peroxidase (GSH-Px) were observed. Proanthocyanidin-rich extract-treated groups showed significantly reduced renal TBA-reactive substance levels and enhanced catalase and GSH-Px activities. These results suggest that proanthocyanidin-rich extract has protective effects against ischemia-reperfusion-induced renal damage associated with oxidative stress.

8) **Yokozawa T., Nakagawa T., Oya T., Okubo T., and Juneja L.R.: Green tea polyphenols and dietary fibre protect against kidney damage in rats with diabetic nephropathy. *J. Pharm. Pharmacol.*, 57: 773-780, 2005.**

Abstract: In this study we examined the effect of green tea polyphenols (GTP) and partially hydrolysed guar gum (PHGG) as dietary fibre on diabetic nephropathy, using rats that had been subjected to subtotal nephrectomy and injection of streptozotocin. The subtotally nephrectomized rats were subjected to resection of three-quarters of the kidney. Rats with diabetic nephropathy were divided into four groups: untreated controls, and animals that received GTP (100 mg kg-1 body weight day-1), PHGG (100 mg kg-1 body weight day-1) and GTP plus PHGG (50 mg kg-1 body weight day-1 plus 50 mg kg-1 body weight day-1). After 50 days of administration, attenuation of urinary protein excretion and the morphological changes peculiar to diabetic nephropathy were observed in all three treated groups. Furthermore, the group treated with GTP plus PHGG showed an improvement of kidney weight and serum levels of urea nitrogen, creatinine and creatinine clearance. Hyperglycaemia, as assessed in terms of blood glucose and glycosylated protein levels, was also improved by administration of GTP plus PHGG. On the other hand, GTP administration increased the activity of superoxide dismutase in the kidney to a significant extent. A significant reduction in the total cholesterol concentration was also observed in the PHGG-treated group. These results suggest that GTP and PHGG could be beneficial as additional therapy in the management of diabetic nephropathy.

9) **Nakagawa T., Yokozawa T., Yamabe N., Rhyn D.Y., Goto H., Shimada Y., and Shibahara N.: Long-term treatment with Hachimi-jio-gan attenuates kidney damage in spontaneously diabetic WBN/Kob rats. *J. Pharm. Pharmacol.*, 57: 1205-1212, 2005.**

Abstract: Diabetes mellitus is now the most common cause of end-stage renal failure. In this study, the effects of Hachimi-jio-gan on diabetic kidney damage in spontaneously diabetic WBN/Kob rats were examined. Oral administration of Hachimi-jio-gan to WBN/Kob rats for 25 weeks significantly suppressed urinary protein excretion. It did not affect body weight loss or blood glucose levels, whereas it reversed the increase in kidney weight of WBN/Kob rats. Hachimi-jio-gan also reduced fibronectin and transforming growth factor beta1 (TGF-beta1) protein expression in the renal cortex. Furthermore, renal lipid peroxidation levels of WBN/Kob rats given Hachimi-jio-gan were significantly lower than those of untreated controls. Renal superoxide dismutase activity was elevated by Hachimi-jio-gan treatment in a dose-dependent manner. These results suggested that Hachimi-jio-gan could prevent diabetic kidney damage by reducing renal oxidative injury and expression of fibronectin and TGF-beta1 proteins, which are all involved in the pathophysiology of diabetic nephropathy.

10) **Goto H., Sasaki Y., Fushimi H., Shibahara N., Shimada Y., and Komatsu K.: Effect of curcuma herbs on vasomotion and hemorheology in spontaneously hypertensive rat. *Am. J. Chin. Med.*, 33: 449-457, 2005.**

Abstract: Curcuma herbs have a vasodilator effect. The effects of C. longa, which induces only endothelium-independent vasodilatation, and C. zedoaria, which induces both endothelium-dependent and -independent vasodilatation, were studied on vasomotion and hemorheology in spontaneously hypertensive rats. Spontaneously hypertensive eight-week-old male rats were assigned to five groups. For 12 weeks, the control group received standard chow. The 3%CL (C. longa) group received standard chow containing 3% (wt/wt) C. longa. The 1%CZ and 3%CZ (C. zedoaria) groups received standard chow containing 1% and 3% (wt/wt) C. zedoaria, respectively. The captoril group received standard chow and 100 mg/kg/day of captoril in drinking water. Blood pressure, vasomotion, hemorheology, etc. were examined. Systolic blood pressure of the 3%CZ and captoril groups decreased significantly as compared to the control group. Acetylcholine-induced endothelium-dependent relaxations of the 3%CZ and captoril groups were increased to a greater degree, significantly, than the control group. When testing xanthine

oxidase-induced contraction, the 3%CZ group was significantly decreased as compared to the control group. Low shear stress of whole blood viscosity showed the 3%CL and 3%CZ groups to be decreased significantly compared to the control group. Thus, Curcuma herbs have hypotensive and protective effect on the endothelium in spontaneously hypertensive rats. Especially, C. zedoaria is more effective than C. longa, and its mechanism is thought to be related to a radical scavenging effect and improvement of hemorheology.

11) **Nakagawa T., Yokozawa T., Kim Y.A., and Tanaka T.: Activity of Wen-Pi-Tang, and purified constituents of Rhei Rhizoma and Glycyrrhizae Radix against glucose-mediated protein damage.** ***Am. J. Chin. Med.*****, 33: 817-829, 2005.**

Abstract: Wen-Pi-Tang, an Oriental medical prescription composed of Rhei Rhizoma, Ginseng Radix, Aconiti Tuber, Zingiberis Rhizoma and Glycyrrhizae Radix, is used clinically as a medicine to treat renal failure. This study was conducted to examine the inhibitory activity of the five crude drug components of Wen-Pi-Tang and several pure compounds isolated from Rhei Rhizoma and Glycyrrhizae Radix against the protein glycation reaction. Rhei Rhizoma exerted the most potent activity, Zingiberis Rhizoma and Glycyrrhizae Radix showed relatively moderate activity, whereas Aconiti Tuber and Ginseng Radix showed weak activity. On the other hand, of 20 compounds obtained from Rhei Rhizoma and Glycyrrhizae Radix, tannins, especially rhatannin, RG-tannin and procyanidin B-2 3,3'-di-O-gallate, showed significantly strong activities that were more effective than the positive control, aminoguanidine. Some flavones such as licochalcone A and licochalcone B, and anthraquinones such as emodin and aloe-emodin, also showed inhibitory activity. These findings may help to explain, at least in part, certain pharmacological activities of Wen-Pi-Tang, whose clinical efficacy against renal failure is already recognized.

12) **Yokozawa T., Cho E.J., Rhyu D.Y., Shibahara N., and Aoyagi K.: Glycyrrhizae Radix attenuates peroxynitrite-induced renal oxidative damage through inhibition of protein nitration.** ***Free Radic. Res.*****, 39: 203-211, 2005.**

Abstract: We investigated the protective effects of Glycyrrhizae Radix extract against peroxynitrite (ONOO-)-induced oxidative stress under in vivo as well as in vitro conditions. The extract showed strong ONOO- and nitric oxide (NO) scavenging effects under in vitro system, in particular higher activity against ONOO-. Furthermore, elevations of plasma 3-nitrotyrosine levels, indicative of in vivo ONOO-generation and NO production, were shown using a rat in vivo ONOO(-)-generation model of lipopolysaccharide injection plus ischemia-reperfusion. The administration of Glycyrrhizae Radix extract at doses of 30 and 60 mg/kg body weight/day for 30 days significantly reduced the concentrations of 3-nitrotyrosine and NO and decreased inducible NO synthase activity. In addition, the nitrated tyrosine protein level and myeloperoxidase activity in the kidney were significantly lower in rats given Glycyrrhizae Radix extract than in control rats. However, the administration of Glycyrrhizae Radix extract did not result in either significant elevation of glutathione levels or reduction of lipid peroxidation in renal mitochondria. Moreover, the in vivo ONOO- generation system resulted in renal functional impairment, reflected by increased plasma levels of urea nitrogen and creatinine, whereas the administration of Glycyrrhizae Radix extract reduced these levels significantly, implying that the renal dysfunction induced by ONOO- was ameliorated. The present study suggests that Glycyrrhizae Radix extract could protect the kidneys against ONOO- through scavenging ONOO- and/or its precursor NO, inhibiting protein nitration and improving renal dysfunction caused by ONOO-.

13) **Hussein G., Nakamura M., Zhao Q., Iguchi T., Goto H., Sankawa U., and Watanabe H.: Antihypertensive and Neuroprotective Effects of Astaxanthin in Experimental Animals.** ***Biol. Pharm. Bull.*****, 28: 47-52, 2005.**

Abstract: Astaxanthin is a natural antioxidant carotenoid that occurs in a wide variety of living

organisms. We investigated, for the first time, antihypertensive effects of astaxanthin (ASX-O) in spontaneously hypertensive rats (SHR). Oral administration of ASX-O for 14 d induced a significant reduction in the arterial blood pressure (BP) in SHR but not in normotensive Wistar Kyoto (WKY) strain. The long-term administration of ASX-O (50 mg/kg) for 5 weeks in stroke prone SHR (SHR-SP) induced a significant reduction in the BP. It also delayed the incidence of stroke in the SHR-SP. To investigate the action mechanism of ASX-O, the effects on PGF(2alpha)-induced contractions of rat aorta treated with NG-nitro-L-arginine methyl ester (L-NAME) were studied in vitro. ASX-O (1 to 10 microM) induced vasorelaxation mediated by nitric oxide (NO). The results suggest that the antihypertensive effect of ASX-O may be due to a NO-related mechanism. ASX-O also showed significant neuroprotective effects in ischemic mice, presumably due to its antioxidant potential. Pretreatment of the mice with ASX-O significantly shortened the latency of escaping onto the platform in the Morris water maze learning performance test. In conclusion, these results indicate that astaxanthin can exert beneficial effects in protection against hypertension and stroke and in improving memory in vascular dementia.

14) **Sekiya N., Kainuma M., Hikiami H., Nakagawa T., Kouta K., Shibahara N., Shimada Y., and Terasawa K.: Oren-gedoku-to and Keishi-bukuryo-gan-ryo inhibit the progression of atherosclerosis in diet-induced hypercholesterolemic rabbits. *Biol. Pharm. Bull.*, 28: 294-298, 2005.**

Abstract: In this study, we examined whether the Kampo formulas Oren-gedoku-to (OGT, Huanglian-jie-du-tang in Chinese) and Keishi-bukuryo-gan-ryo (KBG, Gui-zhi-fu-ling-wan in Chinese) could prevent the progression of atherosclerosis in cholesterol-fed rabbit, an animal model for hypercholesterolemia in vivo. Twenty-four male Japanese white rabbits (2 kg body weight) were divided into four groups. The control group was fed standard rabbit chow containing 1% cholesterol, the OGT group was fed standard rabbit chow containing 1% cholesterol and 1% OGT, the KBG group was fed standard rabbit chow containing 1% cholesterol and 1% KBG, and the vitamin E group was fed standard rabbit chow containing 1% cholesterol and vitamin E (450 mg/1000 g). All four groups were kept on these diets for 8 weeks. At the end of the experiments, the percentage of surface area of the total thoracic aorta with visible plaque was significantly reduced in the OGT and KBG groups. The serum thiobarbituric acid reactive substances of the vitamin E group showed a significantly low value compared with the control group, whereas the serum lipid peroxide levels of the OGT and KBG groups were considerably lower than that of the control groups as well as that of the vitamin E group. Furthermore, the urinary 8-hydroxydeoxyguanosine levels of the OGT and KBG groups were considerably lower than that of the vitamin E group. These results suggest that OGT and KBG prevent the progression of atheromatous plaque by creating a sounder antioxidant defense system than vitamin E.

15) **Hussein G., Goto H., Oda S., Iguchi T., Sankawa U., Matsumoto K., and Watanabe H.: Antihypertensive Potential and Mechanism of Action of Astaxanthin: II. Vascular Reactivity and Hemorheology in Spontaneously Hypertensive Rats. *Biol. Pharm. Bull.*, 28: 967-971, 2005.**

Abstract: The current study was designed to determine the effects of a dietary astaxanthin (ASX-O) on vascular reactivity in spontaneously hypertensive rats (SHR), in order to verify its antihypertensive action mechanism. We evaluated contractions induced by phenylephrine (Phe), angiotensin II (Ang II) and the xanthine/xanthine oxidase (Xan/XOD) system, and relaxations induced by sodium nitroprusside (SNP) as well as endothelium-dependent relaxations mediated by acetylcholine (ACh) in thoracic aorta of the SHR, with and without ASX-O intervention. We also investigated the effects of ASX-O on blood rheology using a microchannel array system. In this study, ASX-O showed a significant modulatory effect on nitric oxide (NO)-induced vasorelaxation by the NO-donor SNP ($p<0.05$). However, it did not show significant effects in restoring the impaired endothelium-dependent relaxation to ACh in the SHR. On the other hand, the constrictive effects by Phe, Ang II and Xan/XOD were ameliorated by ASX-O ($p<0.05$). ASX-O also

demonstrated significant hemorheological effect by decreasing the microchannel transit time of whole blood. In conclusion, the results suggest that ASX-O may act in modulating the blood fluidity in hypertension, and that the antihypertensive effects of ASX-O may be exerted through mechanisms including normalization of the sensitivity of the adrenoceptor sympathetic pathway, particularly [alpha]-adrenoceptors, and by restoration of the vascular tone through attenuation of the Ang II- and reactive oxygen species (ROS)-induced vasoconstriction.

16) **Kiga C., Nakagawa T., Koizumi K., Sakurai H., Shibagaki Y., Ogawa K., Goto H., and Saiki I.: Expression patterns of plasma proteins in spontaneously diabetic rats after oral administration of a Kampo medicine, Hachimi-jio-gan, using SELDI protein chip platform.** ***Biol. Pharm. Bull.*****, 28: 1031-1037, 2005.**

Abstract: We investigated the changes (increase or decrease in peak intensity) in the expression of plasma proteins in spontaneously diabetic WBN/Kob rats that were with complicated diabetic nephropathy, to determine multiple biomarkers in the plasma of diabetic rats. The present study using surface enhanced laser desorption/ionization mass spectrometry (SELDI-TOF-MS) demonstrated that six peaks at mass/charge ratios (m/z) of 4678, 4732, 4808, 9058, 9323, and 9465, among approximately 80 peaks per spectrum in the 2000–10000 Da mass range, had increased peak intensities with the development or progression of diabetic nephropathy in plasma of spontaneously diabetic WBN/Kob rats as compared with those of normal Wistar rats. Administration of the Kampo medicine Hachimi-jio-gan was effective at reducing the expression of diabetic nephropathy but not at reducing blood glucose levels. It also improved the increased levels of these plasma proteins. Other biomarker peaks at m/z 5067, 5279, 7598, and 7917 were not affected by Hachimi-jio-gan administration. Further study will be needed to identify these positive biomarkers and to evaluate the relationship between the efficacy and expression patterns of the plasma proteins in greater detail. The expression patterns of proteins and molecular-related ions revealed that several proteins in plasma may be involved in the development and/or progression of diabetic nephropathy in WBN/Kob rats and the efficacy of Hachimi-jio-gan. This study using ProteinChip technology may provide a useful basis in the search for multiple biomarkers in plasma for the diagnosis of disease and therapeutic evaluation of Kampo medicines.

17) **Cho E.J., Yokozawa T, Kim H.Y., Shibahara N., and Park J.C.: Rosa rugosa attenuates diabetic oxidative stress in rats with streptozotocin-induced diabetes.** ***Am. J. Chin. Med.*****, 32: 487-96, 2004.**

Abstract: The effects of Rosa rugosa on diabetic oxidative stress were investigated using rats with streptozotocin (STZ)-induced diabetes. The diabetic rats showed less body weight gain and heavier kidney and liver weights than normal rats, while the oral administration of Rosa rugosa at a dose of 100 or 200 mg/kg body weight/day for 20 days attenuated the physiological changes induced by diabetes. In addition, administrating Rosa rugosa to diabetic rats resulted in significant and dose-dependent decreases in the serum glucose and glycosylated protein levels, implying that Rosa rugosa improves the abnormal glucose metabolism that leads to oxidative stress. Diabetic rats had higher serum levels of superoxide and nitrite/nitrate. However, the administration of Rosa rugosa dose-dependently reduced the over-production of radicals associated with diabetes, suggesting Rosa rugosa is a radical scavenger that would play a crucial role in protecting against diabetic oxidative stress. Rosa rugosa significantly and dose-dependently reduced thiobarbituric acid-reactive substance levels in serum, hepatic and renal mitochondria, implying that Rosa rugosa would alleviate the oxidative stress associated with diabetes by inhibiting lipid peroxidation. This study provides evidence that Rosa rugosa has potential as a treatment for diabetes through attenuating oxidative stress induced by the diabetic condition.

18) **伏見裕利，織田しのぶ，伊藤隆，柴原直利，喜多敏明，小松かつ子，寺澤捷年：原子吸**

光光度法を聴いた漢薬「石膏」の溶出量に関する研究. ***J. Trad. Med.*, 22; 24-28. 2005.**

Abstract: 漢方処方中で石膏を増減する意義を明らかにする研究の一環として,石膏の水に対する溶解性を,カルシウムの溶出量を指標として原子吸光光度法で検討した.また,剤形の違いが溶出量に及ぼす影響も検討した.さらに,溶出量の他に,溶出実験の前後の石膏,並びに溶出液を再結晶したものについて,結晶構造,無機成分および形態的な変化の有無をX線粉末回折法,蛍光X線分析法および走査電子顕微鏡を用いて検討した.漢方処方中で石膏を用いる場合,さじ加減が意味のあることであった.それは「砕ぎ」石膏を用いた場合にできることで,石膏は再利用可能であり,古来の煎じ方を見直すべきであることが明らかとなった。

19) **Goto H., Kiga C., Nakagawa T., Koizumi K., Sakurai H., Shibagaki Y., Ogawa K., Shibahara N., Shimada Y., and Saiki I.: Effects of two formulations for overcoming oketsu on vascular function and expression patterns of plasma proteins in spontaneously diabetic rats. *J. Trad. Med.*, 22: 237-243, 2005.**

Abstract: We investigated the effects of keishibukuryogan and tokishakuyakusan, which are representative formulations for overcoming oketsu, on vascular function and expression patterns of plasma proteins in spontaneously diabetic rats. Twenty-one- to 24-week-old male WBN/Kob rats were maintained for 18 weeks on a diabetes-accelerated feed, and received standard chow containing 3% (wt/wt) keishibukuryogan or tokishakuyakusan for 25 weeks. There was no significant change in body weight or blood glucose among the groups. Acetylcholine-induced endothelium-dependent relaxation of the keishibukuryogan group significantly increased compared to that of controls. Xanthine/xanthine oxidase-induced contraction of the tokishakuyakusan group and phospholipase A2-induced contraction of the keishibukuryogan and tokishakuyakusan groups significantly decreased compared to the controls. Transit time of whole blood tended to decrease in the tokishakuyakusan group compared to controls. NO2-/NO3- in the keishibukuryogan and tokishakuyakusan groups significantly decreased compared to controls. A study using surface enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS) demonstrated that five and eight peaks had significantly changed peak intensities in plasma of rats treated with keishibukuryogan and tokishakuyakusan, respectively, as compared to the controls. Thus, two representative formulations for overcoming oketsu with different mechanisms of action had favorable effects against vascular dysfunction. Altered plasma protein levels were commonly observed in the rats administered these two formulations. Our study using ProteinChip technology may be useful for the evaluation of the relationship between the efficacy and the profiling of plasma protein expression after administration Kampo medicines, thus leading to the understanding of "Sho" in Kampo medicine.

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◇研究費取得状況

1) 文部科学省科学研究費，萌芽研究（代表：柴原直利，新規）「患者血清のプロテオミクス解析による鍼灸治療効果の客観的評価法の構築」160万
2) 厚生労働科学研究費補助金長寿科学総合研究事業（分担：後藤博三，新規）「高齢者の脳血管障害の進展予防を目的とした漢方薬によるテーラーメード医療の開発」800万
3) 第一銀行奨学財団研究助成（代表：柴原直利，新規）「附子主要成分に及ぼす胃液pHの影響」30万
4) （財）漢方医薬研究振興財団（代表：中川孝子，継続）「和漢薬による糖尿病性腎症進展抑制作用とその作用機序の解明」，50万

◇研究室在籍者

1. 大学院前期２年：中村真依
2. 大学院前期１年：田代いずみ，彌永亜矢乃
3. 長期研修生
   1) 酒本忠幸（医師，鹿児島県，2005，1.1～3.31）
   2) 木村真梨（鍼灸師，大阪府，2005，1.1～3.31）
   3) 花田聖典（大学院薬学研究科臨床薬学修士課程，富山県，2005，1.11～3.12）
   4) 小林功治（大学院薬学研究科臨床薬学修士課程，富山県，2005，1.11～3.12）
   5) 中村真依（大学院薬学研究科臨床薬学修士課程，富山県，2005，1.11～3.12）
   6) 原田秀樹（医師，滋賀県，2005，4.1～3.31）
   7) 廣岡勇之進（医師，長野県，2005，7.1～9.30）
   8) 梁　煜（中医師，中国，2005，11.21～）

4. 短期研修生
   1) 石井宏明（医学生，長野県，2005，1.11～1.28）

2) 小川直美（医学生，長野県，2005，3.28～4.1）
3) 木村知津子（歯科医師，大阪府，2005，4.4～4.15）
4) 藤井恭彦（医学生，鹿児島県，2005，6.6～7.1）
5) 大島壮生（医学生，長野県，2005，7.19～7.22）
6) 秋山拓也（医学生，長野県，2005，7.19～7.29）
7) 吉田将之（薬剤師，富山県，2005，7.25～8.19）
8) 石田弥智（医学生，愛知県，2005，8.15～8.19）
9) 江原洋介（医学生，山口県，2005，8.15～8.19）
10) 堀谷亮介（医学生，大阪府，2005，8.22～8.26）
11) 畝田一司（医学生，神奈川県，2005，8.22～8.26）
12) 瀬戸真由美（薬学院生，熊本県，2005，9.5～9.16）
13) 見上康正（薬学生，熊本県，2005，9.5～9.16）
14) 倉内祐樹（薬学生，熊本県，2005，9.5～9.16）
15) 高石千聖（薬学生，熊本県，2005，9.5～9.16）
16) 向野晃弘（医学生，広島県，2005，9.26～9.30）
17) 松本祐二（医師，島根県，2005，10.24～10.28）
18) 白崎聖子（薬剤師，富山県，2005，10.31～11.11）
19) 横井　正（医師，岡山県，2005，11.21～11.25）