

## 漢方診断学部門 Department of Kampo Diagnostics

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### ◇研究目的 Aims of the research projects

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 Research projects

- 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
  - 各種漢方方剤の指標物質濃度、及びヒトにおける血中濃度の解析
  - 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
  - 糖尿病性腎症に対する桂枝茯苓丸の長期効果の検討
  - 和漢薬の抗酸化作用に関する基礎的研究
- 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
  - 心理テストを利用した証の心理的側面の客観的な評価
  - 漢方医学的病態の自律神経系検査法による解析
  - 漢方医学的病態の品質工学的的手法による解析
- 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
  - 漢方医学研修による教育効果に関する検討
  - 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 Books

- 1) 柴原直利：肝胆脾／血液。「EBM 漢方」，寺澤捷年，喜多敏明編，95-117／121-133，医歯薬出版株式会社，東京，2003.
- 2) 後藤博三：薬物による副作用。「EBM 漢方」，寺澤捷年，喜多敏明編，465-493，医歯薬出版株式会社，東京，2003.
- 3) 酒井伸也：小児科。「EBM 漢方」，寺澤捷年，喜多敏明編，425-440，医歯薬出版株式会社，東京，2003.
- 4) 喜多敏明：精神／骨・関節／麻酔科。「EBM 漢方」，寺澤捷年，喜多敏明編，255-278／281-294／413-421，医歯薬出版株式会社，東京，2003.
- 5) 柴原直利：「証」とは何か／漢方薬使用の留意点。「最新情報「漢方」～あなたに合ったやさしい処方～」，寺澤捷年編，16-21／126-133，NHK出版，東京，2003.
- 6) 喜多敏明：EBMに基づく漢方治療。「最新情報「漢方」～あなたに合ったやさしい処方～」，寺澤捷年編，32-37，NHK出版，東京，2003.
- 7) 後藤博三，寺澤捷年：漢方薬。「治療薬 Up-to-Date2003」，760-762，メディカルレビュー社，東京，2003.

## ◇原著 Original Articles

- 1) **Sakai S., Mantani N., Kogure T., Ochiai H., Shimada Y. and Terasawa K.: Gene Expression of Cell Surface Antigens in the Early phase of Murine Influenza pneumonia Determined by cDNA Expression Array Technique. *Mediat. Inflamm.*, 11: 359-361, 2002.**

**BACKGROUND:** Influenza virus is a worldwide health problem with significant economic consequences. To study the gene expression pattern induced by influenza virus infection, it is useful to reveal the pathogenesis of influenza virus infection; but this has not been well examined, especially in vivo study. **AIMS:** To assess the influence of influenza virus infection on gene expression in mice, mRNA levels in the lung and tracheal tissue 48 h after infection were investigated by cDNA array analysis. **METHODS:** Four-week-old outbred, specific pathogen free strain, ICR female mice were infected by intra-nasal inoculation of a virus solution under ether anesthesia. The mice were sacrificed 48 h after infection and the tracheas and lungs were removed. To determine gene expression, the membrane-based microtechnique with an Atlas cDNA expression array (mouse 1.2 array II) was performed in accordance with the manual provided. **RESULTS AND CONCLUSIONS:** We focused on the expression of 46 mRNAs for cell surface antigens. Of these 46 mRNAs that we examined, four (CD1d2 antigen, CD39 antigen-like 1, CD39 antigen-like 3, CD68 antigen) were up-regulated and one (CD36 antigen) was down-regulated. Although further studies are required, these data suggest that these molecules play an important role in influenza virus infection, especially the phase before specific immunity.

- 2) **Shimada Y., Yang Q., Yokoyama K., Goto H., Kasahara Y., Sekiya N., Hikiami H. and Terasawa K.: Choto-san prevents occurrence of stroke and prolongs life span in stroke-prone spontaneously hypertensive rats. *Am. J. Chin. Med.*, 31: 79-85, 2003.**

The effects of long-term oral administration of choto-san (diao-teng-san in Chinese) extract on the occurrence of stroke and life span were investigated in stroke-prone spontaneously hypertensive rats (SHR-SPs). Twenty-four rats were randomized into three groups. From 8 weeks of age, 0.1% and 0.3% choto-san groups were given water containing 0.1% (150 mg/kg/day) and 0.3% (450 mg/kg/day) choto-san extract, respectively. A control group was given only water. The mean survival times of the control group, 0.1% and 0.3% choto-san groups were 122.1, 159.8 and 176.8 days, respectively. The percent survivals of both the 0.1% and 0.3% choto-san groups were significantly enhanced compared to the control (Kaplan-Meier analysis followed by log-rank test; 0.1% choto-san:  $p < 0.05$ ; 0.3% choto-san:  $p < 0.05$ ). Furthermore, the cumulative percent occurrence of neurological and behavioral signs

accompanying stroke in the 0.3% choto-san group was significantly inhibited compared to the control ( $p < 0.05$ ). These results suggested that choto-san prevents the occurrence of stroke and prolongs the life span of SHR-SPs.

**3) Mantani N., Kogure T., Sakai S., Shimada Y. and Terasawa K.: Reexamination of the relation between menstruation and Kampo diagnosis, Yin-Yang. *Am. J. Chin. Med.* 31: 137-140, 2003.**

Several Chinese herbal medicine textbooks describe that a short menstrual cycle indicates "yang" status and a long cycle indicates "yin" status. However, we sometimes encounter yang patients with a long cycle or yin patients with a short cycle in daily practice. Therefore, we reviewed the relationship between yin-yang and length of menstrual cycle. A questionnaire addressing both menstrual cycle and several parameters for determining yin-yang was completed at the time of the patients' visit to the hospital. Patients were divided into yang or yin groups, and menstrual cycle was compared between the two groups. A short menstrual cycle was mostly observed in yin patients (27.42  $\pm$  1.73, 95% CI: 26.32-28.52,  $n = 12$ ) and a long cycle was mostly observed in yang patients (31.63  $\pm$  3.96, 95% C.I: 29.51-33.74,  $n = 16$ ). The difference in menstrual cycle between the two groups was significant ( $p = 0.002$ ), and this result was entirely opposite to the traditional theory. This study identified a discrepancy between the traditional theory and the actual menstrual cycle findings in this small population. Current reexamination of the relationship between yin-yang and menstruation in a larger population is warranted.

**4) Goto H., Shimada Y., Tanikawa K., Sato S., Hikiami H., Sekiya N., Terasawa K.: Clinical evaluation of the effect of traditional herbal medicines containing Daio (Rhei Rhizoma) on the progression of diabetic nephropathy with overt proteinuria. *Am. J. Chin. Med.* 31:267-275,2003.**

We studied the effect of traditional herbal medicines containing daio (Rhei Rhizoma) on the long-term progression of diabetic nephropathy with overt proteinuria in eight patients [mean age 60 (45-73) years; duration of diabetes 18 (7-36) years]. At the beginning of the study, mean HbA1c was 8.2% and mean serum creatinine was 1.0  $\pm$  0.3 mg/dl. Every patient had diabetic neuropathy and retinopathy. Three of the patients had hypertension and four had ischemic heart disease. After 107  $\pm$  25 months, the mean serum creatinine level had significantly increased to 4.8  $\pm$  2.6 mg/dl. The mean serum creatinine levels of five patients not advancing to dialysis treatment increased from 1.2  $\pm$  0.3 to 3.2  $\pm$  1.0 mg/dl, and the three patients requiring dialysis increased from 0.8  $\pm$  0.1 to 7.5  $\pm$  2.1 mg/dl. In the control group, treated without traditional herbal medicines, the mean serum creatinine level had significantly increased from 1.0  $\pm$  0.3 to 9.5  $\pm$  1.9 mg/dl after 71  $\pm$  12 months. All of the control group required dialysis treatment. Diabetic nephropathy with overt proteinuria is reported to develop into renal failure after 6-7 years. In this retrospective study, traditional herbal medicines with Daio were considered to be effective in prolonging the pre-dialysis period of diabetic nephropathy.

**5) Sasaki Y., Goto H., Tohda C., Hatanaka F., Shibahara N., Shimada Y., Terasawa K., Komatsu K.: Effects of Curcuma Drugs on vasomotion in isolated rat aorta. *Biol. Pharm. Bull.* 26(8): 1135-1143, 2003.**

The effectiveness of Curcuma drugs against "Oketsu" and the differences in their efficacy were evaluated by examining their vasomotional effects as one index. Since nitric oxide (NO) is the relaxation factor of vascular smooth muscle and also an inhibitor of platelet aggregation in blood vessels, substances showing NO-dependent relaxation are thought to be effective in improving Oketsu. In this study, five Curcuma drugs derived from *Curcuma longa*, *C. kwangsiensis*, *C. phaeocaulis*, *C. wenyujin*, and *C. zedoaria* were used. Methanol extracts exhibited intense effects on relaxation in rings precontracted by prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) despite pretreatment with and without NG-nitro-L-arginine methyl ester (L-NAME) as an inhibitor of NO synthesis. The maximal activities were approximately 80% at 10<sup>-3</sup> g/ml. From these methanol extracts, curcumin and eight sesquiterpenes were isolated. Since all these

compounds showed NO-independent relaxation effects with almost the same intensities, the relaxation effects of *Curcuma* drugs can be estimated by the total amounts of curcumin and sesquiterpenes. Polysaccharides, the main constituents of methanol-insoluble compounds of water extracts, in contrast, showed contraction effects; only polysaccharides in *C. zedoaria* showed NO-dependent relaxation as well as contraction. All water extracts showed relaxation effects as sum of the methanol-soluble compounds-induced relaxation and polysaccharides-induced contraction. Therefore, all *Curcuma* drugs tested in the present study can be effective for vasodilation. Moreover, the derived from *C. zedoaria* has potential to cure Oketsu with its various acting points.

**6) Yokozawa T., Cho EJ., and Nakagawa T.: Influence of green tea polyphenol in rats with arginine-induced renal failure. *J. Agric. Food Chem.* 51: 2421-2425, 2003.**

To determine whether green tea polyphenol ameliorates the pathological conditions induced by excessive dietary arginine, green tea polyphenol was administered to rats at a daily dose of 50 or 100 mg/kg body weight for 30 days with a 2% w/w arginine diet. In arginine-fed control rats, urinary and/or serum levels of guanidino compounds, nitric oxide (NO), urea, protein, and glucose increased significantly, while the renal activities of the oxygen species-scavenging enzymes superoxide dismutase (SOD) and catalase decreased, compared with casein-fed rats. However, rats given green tea polyphenol showed significant and dose-dependent decreases in serum levels of creatinine (Cr) and urea nitrogen and urinary excretion of Cr, and they exerted a slight reduction of nitrite plus nitrate, indicating that green tea polyphenol reduced the production of uremic toxins and NO. In addition, in arginine-fed rats the urinary urea, protein, and glucose level increases were reversed by the administration of green tea polyphenol. Moreover, in rats given green tea polyphenol the SOD and catalase activities suppressed by excessive arginine administration increased dose-dependently, implying the biological defense system was augmented as a result of free radical scavenging. These results suggest that green tea polyphenol would ameliorate renal failure induced by excessive dietary arginine by decreasing uremic toxin, and NO production and increasing radical-scavenging enzyme activity.

**7) Yokozawa T., Rhyu DY., Cho EJ. and Aoyagi K.: Protective activity of (-)-epicatechin 3-O-gallate against peroxynitrite-mediated renal damage. *Free Radical Research* 37: 561-571, 2003.**

The protective effect of (-)-epicatechin 3-O-gallate (ECg) against peroxynitrite (ONOO<sup>-</sup>)-mediated damage was examined using an animal model and a cell culture system. In rats subjected to lipopolysaccharide (LPS) administration plus ischemia-reperfusion, the plasma 3-nitrotyrosine level an indicator of ONOO<sup>-</sup> production in vivo, was elevated, whereas it declined significantly and dose-dependently after the oral administration of ECg at doses of 10 and 20 micromoles/kg body weight/day for 20 days prior to the process. Moreover, oral administration of ECg significantly enhanced the activities of the antioxidant enzymes, superoxide dismutase, catalase and glutathione peroxidase, and the antioxidant glutathione, showing enhancement of the biological defense system against the damage induced by ONOO<sup>-</sup>. In addition, the significant increase in the renal mitochondrial thiobarbituric acid-reactive substance level of LPS and ischemic-reperfused control rats was attenuated in rats given ECg. Furthermore, the elevations in the plasma urea nitrogen and creatinine (Cr) levels and the urinary methylguanidine/Cr ratio induced by the procedure were attenuated markedly after oral administration of ECg, implying amelioration of renal impairment. The addition of ECg (25 or 125 microM) prior to 3-morpholinosydnonimine (SIN-1, 800 microM) exposure reduced ONOO<sup>-</sup> formation and increased the viability of cultured renal epithelial (LLC-PK1) cells in a dose-dependent manner. In particular, ECg inhibited ONOO<sup>-</sup>-mediated apoptotic cell death, which was confirmed by decreases in the DNA fragmentation rate and the presence of apoptotic morphological changes, i.e. small nuclei and nuclear fragmentation. Furthermore, adding ECg before SIN-1 treatment regulated the cell cycle by enhancing G2/M phase arrest. This study provides evidence that ECg has protective activity against the renal damage induced by excessive ONOO<sup>-</sup> in

cellular and in vivo systems.

**8) Yokozawa T., Kim H.Y., Cho E.J., Yamabe N., and Choi J.S.: Protective effects of mustard leaf (*Brassica juncea*) against diabetic oxidative stress. *J. Nutr. Sci. Vitaminol.*, 49: 87-93, 2003.**

Of four fractions (CH<sub>2</sub>Cl<sub>2</sub>, EtOAc, BuOH and H<sub>2</sub>O) from mustard leaf (*Brassica juncea*), the EtOAc fraction showed the strongest inhibitory effects, which were concentration-dependent, on the formation of advanced glycation end products and free radical-mediated protein damage in an in vitro system, indicating that this fraction has a potential protective role against diabetes and/or its complications. Based on these results, we carried out an in vivo study to determine whether the EtOAc fraction protected against diabetic oxidative stress induced by streptozotocin. Oral administration of the EtOAc fraction at doses of 50 and 200 mg/kg body weight/d for 10 d reduced the serum levels of glucose and glycosylated protein, implying that the impaired glucose metabolism due to diabetes had been ameliorated. In addition, the EtOAc fraction significantly reduced the thiobarbituric acid-reactive substance levels of serum and hepatic and renal mitochondria. Furthermore, the elevated levels of superoxide and nitrite/nitrate were reduced in a dose-dependent manner by oral administration of the EtOAc fraction. These findings suggest that the EtOAc fraction from mustard leaf might be beneficial in attenuating the damage caused by oxidative stress involved in diabetes and its complications.

**9) Yokozawa T., Ishida A., Cho E.J. and Nakagawa T.: The effects of *Coptidis Rhizoma* extract on a hypercholesterolemic animal model. *Phytomedicine* 10: 17-22, 2003.**

The serum cholesterol (total, free, esterified, low density lipoprotein (LDL) and oxidized LDL) levels of rats fed a diet containing, by weight, 1% cholesterol and 0.5% cholic acid increased, as compared with those of rats fed a normal diet. The levels, especially of total cholesterol, LDL and oxidized LDL, were reduced significantly in a dose-dependent manner, in rats given *Coptidis Rhizoma* extract orally at doses of 50 and 100 mg/kg body wt./day for 30 days. These results indicate that *Coptidis Rhizoma* extract is effective in reducing the pathological damage caused by hypercholesterolemia, through lowering of serum cholesterol levels. In addition, *Coptidis Rhizoma* extract reduced the level of liver cholesterol, but it did not reduce that of fecal cholesterol, suggesting that the cholesterol level-lowering effect resulted from the reduction of cholesterol synthesis, not the enhancement of its excretion. Furthermore, the serum thiobarbituric acid-reactive substance level decreased after oral administration of *Coptidis Rhizoma* extract, indicating that *Coptidis Rhizoma* could prevent hypercholesterolemic disease through reducing lipid peroxidation. This study demonstrates that *Coptidis Rhizoma* may be a useful therapy for hypercholesterolemia through reducing oxidative stress and cholesterol levels.

**10) Tanaka N., Sekiya N., Hattori M., Goto H., Shibahara N., Shimada Y. and Terasawa K.: Measurement of plasma procyanidin B-2 and procyanidin B-3 levels after oral administration in rat. *Phytomedicine* 10: 122-126, 2003.**

Using a high-performance liquid chromatographic method and mass spectrometry analysis, we successfully measured the absorption of orally administered procyanidin B-2 and procyanidin B-3 isolated from *Cinnamomum cortex* (the bark of *Cinnamomum cassia* Blume) in the rat plasma. This method used a TSK- GEL ODS-80TS column, two solvents (A: 0.01% acetic acid; B: methanol with 0.01% acetic acid) in a linear gradient at a flow-rate of 1.0 ml/min, and fluorescence detection at excitation and emission wavelengths of 220 and 327 nm.

**11) Hikiami H., Goto H., Sekiya N., Hattori N., Sakakibara I., Shimada Y. and Terasawa K.: Comparative efficacy of Keishi-bukuryo-gan and pentoxifylline on RBC deformability in patients with "oketsu" syndrome. *Phytomedicine*, 10: 459-466, 2003.**

Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan) (KBG) is one of the prescriptions in Japanese traditional medicine for improving the "oketsu" syndrome, so-called blood stasis syndrome. "Oketsu" syndrome is an important pathological conception in Japanese traditional medicine and often accompanies cerebro-vascular disorders. Previously, we were able to reveal a deterioration of RBC (Red blood cell) deformability and viscoelasticity in patients with "oketsu" syndrome. The purpose of the present study was to evaluate whether KBG has an effect on RBC deformability in comparison with pentoxifylline (PXF). The subjects were 30 male patients with multiple lacunar infarctions. Eighteen patients (44-79 yrs, mean +/- SD, 66.1 +/- 10.7 yrs) were treated with 12 g of KBG daily for 4 weeks (KBG group). Twelve patients (59-78 yrs, 70.7 +/- 6.4 yrs) were treated with 300 mg of PXF daily for 4 weeks (PXF group). Based on the "oketsu" score, the patients of each group were divided into two subgroups, a non-"oketsu" group ("oketsu" score 20 points or less) and an "oketsu" group ("oketsu" score 21 points or higher). KBG had significant effects on RBC deformability as evaluated by filtration method. KBG also significantly increased intracellular ATP content, as did PXF. Moreover, KBG was more effective for patients with a more severe "oketsu" state. However, PXF was effective only in patients with "oketsu" syndrome, who might have deteriorated RBC deformability. In conclusion, the effect of KBG on RBC deformability was by no means inferior to PXF.

**12) Cho EJ., Yokozawa T., Rhyu DY., Kim SC., Shibahara N. and Park JC.: Study on the inhibitory effects of Korean medicinal plants and their main compounds on the 1,1-diphenyl-2-picrylhydrazyl radical. *Phytomedicine*, 10: 544-551, 2003.**

A 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-generating system was used to evaluate the antioxidant properties of Korean medicinal plants that have been used widely as folk medicines for several disorders, as well as compounds isolated from them. Among the Rosaceae, *Rosa rugosa* and *Rosa davurica* showed strong DPPH radical-scavenging activity. The most effective medicinal plant from families other than Rosaceae was *Cedrela sinensis*, followed in order by *Nelumbo nucifera*, *Eucommia ulmoides*, *Zanthoxylum piperitum*, *Cudrania tricuspidata* and *Houttuynia cordata*. These results serve as a good index of the free radical-scavenging activities of Korean medicinal plants. Furthermore, the polyphenols isolated from these plants, procyanidin B-3, (+)-catechin, gallic acid, methyl gallate, quercetin, quercetin-3-O-beta-D-glucoside, quercetin-3-O-beta-galactoside, quercetin-3-O-rutinoside and kaempferol, exerted strong DPPH radical-scavenging activity. These results suggest that the Korean medicinal plants and the polyphenols isolated from them that exhibited effective radical-scavenging activity may be promising agents for scavenging free radicals and treating diseases associated with excess free radicals.

**13) Sekiya N., Shibahara N., Sakakibara I., Hattori N., Goto H. and Terasawa K.: Inhibitory Effects of Oren-gedoku-to (Huanglian-Jie-Du-Tang) on Free Radical-induced Lysis of Human Red Blood Cells. *Phytother. Res.*, 17: 147-151, 2003.**

Oren-gedoku-to (Huanglian-Jie-Du-Tang, OGT) has been used for the treatment of cerebrovascular disease, hypertension, gastritis and liver disease in Japan. The present study was to test our hypothesis that ingestion of Oren-gedoku-to extract (TJ-15) would protect red blood cell (RBC) membrane from free radical-induced oxidation if antioxidants in OGT could be absorbed and circulated in blood. When incubated with RBC suspension, OGT and its four constituting herbs provided strong protection for RBC membrane to hemolysis induced by 2,2-azo-bis (2-amidinopropane) dihydrochloride (AAPH), an azo free radical initiator. The inhibitory effect was in a dose-dependent manner at concentrations of 5 microgram/ml to 500 microgram/ml. Furthermore, the ingestion of 7.5 g of OGT (daily dose) was associated with a significant decrease in susceptibility of RBC to hemolysis in humans. The direct protection of RBC membrane from free-radical attack as observed in the present study could provide an important pathophysiological basis for making use of the favorable hemorheological effect of OGT.

- 14) Sekiya N., Goto H., Shimada Y., Endo Y., Sakakibara I. and Terasawa K.: Inhibitory effects of triterpenes isolated from Hoelen on free radical-induced lysis of human red blood cells. *Phytother. Res.*, 17:160-162,2003.

Hoelen, scleroderma of *Poria cocos* Wolf, has long been used as a sedative and diuretic in traditional medicine. Formerly, we demonstrated that Hoelen in vitro protects red blood cells from AAPH-induced hemolysis. In this study, tests were carried out to identify the main ingredient of Hoelen that has the scavenging effect on free-radicals. Triterpene carboxylic acids isolated from the methanol extract of Hoelen, i.e. pachymic acid, polyporenic acid, 3-epidehydrotumulosic acid, 3beta-hydroxylanosta-7,9(11), 24-trien-21-oic acid and 3-o-acetyl-16 alpha-hydroxytrametenolic acid, were found to have inhibitory activities against AAPH-induced lysis of red blood cells.

- 15) Kim H.Y., Yokozawa T., Cho E.J., Cheigh H.S., Choi J.S., and Chung H.Y.: In Vitro and in Vivo Antioxidant effects of mustard leaf (*Brassica Juncea*). *Phytother. Res.*, 17: 465-471, 2003.

To investigate the antioxidant activity of mustard leaf (*Brassica juncea*), we prepared four fractions (CH<sub>2</sub>Cl<sub>2</sub>, EtOAc, BuOH and H<sub>2</sub>O fractions) and examined their radical scavenging activities in vitro and in vivo. Based on the in vitro results of spin trapping and 1,1-diphenyl-2-picrylhydrazyl radical, we carried out an in vivo study with the BuOH fraction to investigate its effect on oxidative stress in rats with streptozotocin-induced diabetes. We found that in comparison with untreated diabetic control rats, oral administration of the BuOH fraction (100 or 200 mg/kg body weight/day for 10 days) induced a significant decrease in serum glucose and glycosylated protein, which is glycosylated with hemoglobin as an indicator of oxidative stress. Moreover, administration of the BuOH fraction also effectively reduced the serum superoxide and nitrite/nitrate levels. Furthermore, the levels of thiobarbituric acid-reactive substances in serum and liver were also significantly lower than in the control group. These results indicate that the BuOH fraction of mustard leaf controls glucose metabolism and reduces lipid peroxidation as well as the level of oxygen radicals, ameliorating the damage caused by oxidative stress in diabetes.

- 16) Shibahara N., Shimada Y., Sekiya N., Goto H., Mantani N., Tahara E. and Terasawa K.: Effect of Keishi-bukuryo-gan on autonomic nervous activity. *J. Trad. Med.* 20: 62-67, 2003.

In order to confirm any effects of Keishi-bukuryo-gan (KBG) on the autonomic nervous system, 8 healthy volunteers were evaluated with laser Doppler flowmetry and spectral analysis of the R-R intervals (RR) and systolic blood pressure (SBP). After evaluation of the *koketsu* score and measurement of the electrophysiological parameters (PRE), each subject was administered KBG or hot water. The same parameters were re-measured at 15, 30, 45, 60 and 90 minutes after their administration in each subject. Changes in the parameters after the administration of KBG or hot water were investigated compared with PRE. In the experiment with KBG, skin blood flow (SBF) was increased at 90 min, although it had been significantly decreased at 15 min. By spectral analysis, SBP- low frequency (LF) and SBP- low to high frequency ratio (L/H) were initially increased at 15 min, and then were significantly decreased at 60 and 90 min. As for hot water, there were no significant changes in any of the parameters. It is known that SBF changes with sympathetic nervous activity, and SBP-LF and SBP-L/H reflect sympathetic nervous activity. These results suggest that KBG has certain effects on sympathetic nervous activity.

- 17) Nakagawa T., Yokozawa T., Oowada S., Goto H., Shibahara N., Shimada Y. and Terasawa K.: Amelioration of kidney damage in spontaneously diabetic WBN/Kob rats after treatment with Keishi-bukuryo-gan. *J. Trad. Med.*, 20: 156-164, 2003.

In this study, we investigated whether Keishi-bukuryo-gan can retard the occurrence and progression of diabetic nephropathy in spontaneously diabetic WBN/Kob rats. Administration of Keishi-bukuryo-gan did not affect body weight loss or blood glucose levels but effectively lowered urinary protein excretion and serum creatinine levels, and ameliorated glomerular, vascular and tubulointerstitial lesions. In addition, treatment of the diabetic rats with Keishi-

bukuryo-gan reduced renal levels of thiobarbituric acid reactive substances and advanced glycation end products significantly and elevated renal superoxide dismutase activity significantly. These results suggest that Keishi-bukuryo-gan exerts antioxidant effects in the kidneys of diabetics and may prove that the herbal medicine is useful for inhibiting the progression of diabetic kidney disease.

**18) Kogure T. Mantani N. Sakai S. Shimada Y. Tamura J. and Terasawa K.: Natural killer cytolytic activity is associated with the expression of killer cell immunoglobulin-like receptors on peripheral lymphocytes in human. *Mediat. Inflamm.*, 12: 117-21, 2003.**

Although it has been shown that killer cell immunoglobulin-like receptors (KIRs) on peripheral lymphocytes are upregulated by interleukin-2 (IL-2), which activates natural killer (NK) activity, it has not been demonstrated whether the expression of KIRs is related to NK activity. Therefore, we investigated the association between the KIR expression on lymphocytes and NK activity. CD158a/b expression on lymphocytes obtained from 37 subjects was analyzed using flow cytometry. Simultaneously, NK activity was measured each sample using a  $^{51}\text{Cr}$ -release assay. Additionally, lymphocytes were cultured in RPMI 1640 medium with or without IL-2 for 48 h, and then their CD158a/b expression and NK activity was analyzed. CD158a/b expression was significantly correlated with NK activity. Especially, the percentage of CD16+CD158a+ and CD8+CD158a/b+ cells in lymphocytes showed a highly significant correlation with NK activity. However, analysis of CD8+ and CD16+ cells revealed that there was only a significant correlation between the percentage of CD8+CD158a+ cells among only CD8+ cells and NK activity. The upregulation of CD16+CD158a/b+ cells in response to IL-2 tended to be related to the increase of NK activity, but the relationship was not significant. In conclusion, the level of KIR expression was correlated with NK activity, and IL-2 treatment resulted in an increase of NK activity as well as KIR expression, suggesting that upregulation of KIRs enhances the ability to sort target cells, such as virus-infected cells from uninfected cells, according to major histocompatibility complex class I expression.

**19) 松浦 伸, 柴原直利, 伊藤 隆, 伏見裕利, 小暮敏明, 後藤博三, 嶋田 豊, 寺澤捷年: 煎出時における生薬の吸水量に関する検討. *日本東洋医学雑誌*, 54: 199-208, 2003.**

頻用処方構成する75種類の生薬を対象として、煎剤作成時における個々の生薬の吸水量を検討した。煎じ容器に水道水600mlを入れて加熱沸騰後に各生薬10gを加え、70分間煎じた後に60分間静置して再度20分間加熱した。生薬を加えた時間の10,20,30,40,60,130,150分後の吸水量を測定し、又、各時点での吸水量における最大値をその生薬の最大吸水量とした。植物生薬における最大吸水量の最大値は菊花69.10g、最低値は桃仁3.26gであり、その平均値は $22.51 \pm 13.00\text{g}$ と個々の生薬の吸水量には多くの差を認めた。経時的には60種類の生薬では吸水量が煎じ開始10分後あるいは20分後に最大吸水量の80%以上を示したが、8種類の生薬では煎じ時間と共に吸水量が増加した。

**20) 日高隆雄, 内尚子, 齋藤滋, 喜多敏明, 柴原直利, 寺澤捷年: 更年期障害に対する桂枝茯苓丸及び加味逍遙散の効果. *産婦人科漢方研究のあゆみ*, 7: 37-41, 2003.**

更年期障害に対して頻用される桂枝茯苓丸及び加味逍遙散の臨床効果を検討し、どのような症例に対してこれらの漢方処方が有効であるのかを自覚的な更年期症状の内容、程度から検討した。桂枝茯苓丸及び加味逍遙散は、いずれも更年期障害患者が訴える血管運動神経症状と精神神経症状の両方にバランスよく効果を発揮する使い易い方剤である。「顔のほてり」や「不眠」を強く訴える症例に対しては桂枝茯苓丸、「憂うつ」や「不眠」を強く訴える症例に対しては加味逍遙散が有効である。非特異的な息切れ・動悸・肩こり・腰痛を強く訴えるような症例に対してはいずれの処方も無効となる可能性が高い。



21) 奥田忠行, 松井祥子, 柴原直利, 関根道和, 上野智浩, 大門良男, 北島勲: 血液ガス分析機器の相違による Pco<sub>2</sub> 値乖離の検討. 臨床検査, 47: 553-558, 2003.

検査部, 緊急部に各々1台ずつ血液ガス分析機器が設置され, 設置当初から精度管理を毎日実施し, 更にメンテナンス等も使用書に準じて行っていた。臨床医からの指摘により動脈血炭酸ガス分圧値 (PCO<sub>2</sub>) がメーカー間で乖離している事例に遭遇した。コントロール, 血液ガス標準物質, トノメトリー試験を用いて原因を検討した。血液ガス検体で, pH 値, 酸素ガス分圧値 (PO<sub>2</sub>) は類似した値であった。PCO<sub>2</sub> 値のみ, Bayer 社がラジオメーター社より高値であった。原因は, 標準物質とトノメトリー試験より Bayer 社のリストラクター自体にあることがわかった。PCO<sub>2</sub> 値の乖離の原因追求にはトノメトリー試験と血液ガス標準物質の測定が有用であった。

22) 柴原直利, 矢野耕也, 関矢信康, 嶋田 豊, 寺澤捷年, 矢野 宏: 漢方問診データの MT システムによる定量化の研究 (1) - MT システムの適用の可能性と証のデータの定量化 -。品質工学, 5: 78-85, 2003.

漢方医学における病態診断の尺度の一つに「気血水」の病態があるが, これは医師の経験や知識に基づく高度なパターン認識である。これに関して, 受診者の問診データから単位空間を作成し, 瘀血病態に対し, 逆行列法でマルチ空間を作成した MMT 法に基づいたマハラノビスの距離によった診断・判別を検討した。問診データは, 項目数よりもデータ数が多いため, 医学的に意味のある群を作り単位空間を複数作成し, マルチのマハラノビスの距離を求めた。その結果, 健常者群に対して非健常者の距離は, 非常に高い判別性を示すことができ, 瘀血患者の診断について数量化をすることが可能になった。このことは, 和漢診療学の診断に新しい指針を与える可能性を示唆するものである。

23) 柴原直利, 矢野耕也, 関矢信康, 嶋田 豊, 寺澤捷年, 矢野 宏: 漢方問診データの MT システムによる定量化の研究 (2) - 証のデータの定量化における MMT 法と MMTA 法の比較 -。品質工学, 5: 86-91, 2003.

漢方の診断においては, 患者の「証」を正しく診断することが重要となるが, 今までは医師の経験知により行われている要素が大きかった。ここでは患者の「証」を一種のパターンとして捉え, MT 法をパターン認識の一手法として応用し, 瘀血といわれる一群の患者の診断を試みた。200以上ある問診項目を15の大項目に分け, それに基づいたマルチ行列を, 逆行列法 (MT法) と余因子行列法 (MTA法) の2通りの方法に分けて解析を行い, MMT 法と MMTA 法の比較という形で対比させた。結果的にどちらの手法を用いても非健常者の距離が離れ, 同様の結果が導かれるということが明らかとなり, 計数値のみで構成された医学データの解析法に指針を与えたといえる。

24) 柴原直利, 矢野耕也, 関矢信康, 嶋田 豊, 寺澤捷年, 矢野 宏: 漢方問診データの MT システムによる定量化の研究 (3) - 証のデータの定量化における多階 MMTA 法 -。品質工学, 6: 40-45, 2003.

漢方の診断では個々の病態診断が重要である。筆者らはその病態診断を一種のパターンとして捉え, パターン認識の一手法として MT 法を応用し, 「瘀血」といわれる一群の患者の診断を試みてきた。瘀血病態の診断精度については, MMTA 法の SN 比を検討することが重要であるが, 精度向上の方法論として多階 MT 法が提示されていることから, 1階の MMTA 法と3階の MMTA 法の SN 比に分けて解析を行ない, 診断の精度について対比を行なった。その結果, 3階の SN 比の利得が大きく得られており, 漢方医学的な診断の精度の向上に寄与ができたものと考えられる。

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- 1) 厚生科学研究費補助金（長寿科学総合研究事業）「高齢者の脳血管障害の予防と進展防止を目的とした漢方薬による治療法の開発」（継続，後藤分担）40万
- 2) 和漢薬・バイオテクノロジー研究「富山県で栽培可能な生薬に関する総合的研究」（新規，柴原代表，後藤分担）250万

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- 1) 永嶺 宏一（医師，千葉県，2003，3～8）
- 2) 堀江 延和（医師，和歌山県，2003，4～12）
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