

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) 喜多敏明：五臓六腑。「入門漢方医学」日本東洋医学会学術教育委員会編集。南江堂，東京，pp51-55，2002。
- 2) 後藤博三，寺澤捷年：漢方薬。「治療薬 Up-to-Date 2002」，メディカルレビュー社，東京，pp736-739，2002。
- 3) 後藤博三，関矢信康：循環器疾患と EBM，高脂血症・糖尿病を中心に。「漢方治療における EBM—その現状と展望—」。PROGRESS IN MEDICINE，ライフサイエンス，東京，pp39-44，2002。

◇原著 Original Articles

- 1) **Yang Q., Goto H., Shimada Y., Kita T., Shibahara N. and Terasawa K.: Effects of Choto-san on hemorheological factors and vascular function in stroke-prone spontaneously hypertensive rats. *Phytomedicine*, 9 : 93-98, 2002.**

Abstract: Choto-san is a formula used for the treatment of headache and vertigo. Recently it has often also been used for hypertension and dementia. One of the mechanisms involved is thought to be the improvement of blood circulation, but the details are still unclear. In this study, the effect of Chotosan was studied on nitric oxide (NO) function, hemorheological factors and endothelial function in stroke-prone spontaneously hypertensive rats (SHR-SP). Rats were given Choto-san in drinking water for eight weeks. Body weight, blood pressure, serum NO₂-/NO₃-, lipid peroxides, blood viscosity, erythrocyte deformability and endothelium-dependent/-independent relaxation were measured. The results indicated that Choto-san caused a decrease in blood pressure and an increase in erythrocyte deformability and NO function. Blood viscosity was not changed. Furthermore, endothelium-dependent relaxation by acetylcholine was significantly increased as compared to control. In this study, it was supposed that Choto-san had a protective effect on the endothelium. SHR-SP is a useful model for human brain stroke, and Choto-san showed a protective effect against cerebral vascular injury in the susceptible rat.

- 2) **Mantani N., Kogure T., Sakai S., Goto H., Shibahara N., Kita T., Shimada Y. and Terasawa K.: Incidence and clinical features of liver injury related to Kampo (Japanese herbal) medicine in 2,496 cases between 1979 and 1999: problems of the lymphocyte transformation test as a diagnostic method. *Phytomedicine*, 9 : 280-287, 2002.**

Abstract: We retrospectively examined the summaries of all admission records of patients from 1979 to 1999 in our department, and selected for further study all liver injuries suspected of being related to Kampo medicines. Among 2,496 summaries, 30 summaries described liver disorders suspected of being related to Kampo medicines. Whether there was a causal relationship between the use of Kampo medication and the occurrence of liver injury was assessed according to the criteria described by Haller and Benowitz (2000), independently of the results of the lymphocyte transformation test (LTT). Among 30 events, we concluded that 9 were definitely unrelated, and 6 were probably unrelated to the use of Kampo medicines. Nine events (0.36% of 2,496 patient admissions and 0.06% of 14,616 outpatients) were considered possibly related, and only 6 events (0.24% of 2,496 patient admissions and 0.04% of 14,616 outpatients) were judged to be definitely or probably related to Kampo medicines. Low-grade eosinophilia was observed in a few patients of these "related" groups, and no fever or rash was observed in these "related" groups. Other clinical features, including type of liver injury, duration of Kampo medicine-use, recovery period and laboratory data, were not different from liver injuries associated with western drugs. Most patients in the definitely "unrelated" group were positive in the LTT for the suspect Kampo medicine, suggesting that the LTT may be unreliable for the diagnosis of Kampo-medicine-induced liver injury. From 1979 to 1999, our use of Kampo medicines to treat patients resulted in a low rate of liver injury and no fatalities.

- 3) Sekiya N., Kogure T., Kita T., Kasahara Y., Sakakibara I., Goto H., Shibahara N., Shimada Y. and Terasawa K.: **Reduction of plasma triglyceride level and enhancement of plasma albumin concentration by Oren-gedoku-to administration.** *Phytomedicine*, 9 : 455-460,2002.

Abstract: 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 whether ingestion of OGT extract (TJ-15) would affect the metabolism of fatty acids and the usual antioxidant molecule (such as albumin, uric acid and bilirubin) levels in human plasma. After the administration of TJ-15, plasma total cholesterol and the triglyceride level significantly decreased, and lipoprotein lipase mass increased. Significant enhancement of plasma albumin level and reduction of the total plasma protein level resulted in an increment of the albumin/globulin ratio. Plasma fibrinogen, an independent risk factor for cerebrovascular disease, declined considerably, but the reduction was not statistically significant. The findings of this study suggest that ingestion of TJ-15 improves the microcirculation through lipid and protein metabolisms, and is useful for the treatment of cerebral vascular attack in human.

- 4) Sekiya N., Shimada Y., Shibahara N., Takagi S., Yokoyama K., Kasahara Y., Sakakibara I. and Terasawa K.: **Inhibitory effects of Choto-san (Diao-teng-san), and hooks and stems of Uncaria sinensis on free radical-induced lysis of rat red blood cells.** *Phytomedicine*, 9 : 636-640, 2002.

Abstract: The present study is designed to test our hypothesis that the ingestion of *Uncaria sinensis* (US), the main medicinal plant of Choto-san (Diao-teng-san, CS), would protect red blood cell (RBC) membrane from free radical-induced oxidation if polyphenolics in US could be absorbed and circulated in blood. When incubated with RBC suspension, Choto-san extract (CSE) and *Uncaria sinensis* extract (USE) exhibited strong protection for RBC membrane against hemolysis induced by 2,2-azo-bis (2-amidinopropane) dihydrochloride (AAPH), an azo free-radical initiator. The inhibitory effect was dose-dependent at concentrations of 50 to 1000 microg/mL. Ingestion of 200 mg of USE was associated with a significant decrease in susceptibility of RBC to hemolysis in rats. Furthermore, caffeic acid, an antioxidative hydroxycinnamic acid, was identified in rat plasma after administration of URE.

- 5) Sekiya N., Goto H., Shimada Y., Terasawa K.: **Inhibitory effects of Keishi-bukuryo-gan on free radical induced lysis of rat red blood cells.** *Phytotherapy Research*, 16 : 373-376, 2002.

Abstract: Keishi-bukuryo-gan (KBG) prevents the progression of atherosclerosis in cholesterol-fed rabbits by its antioxidative effect. The present study was to test our hypothesis that ingestion of KBG would protect red blood cell (RBC) membranes from free radical induced oxidation if polyphenolic antioxidants in KBG could be absorbed and circulated in the blood. When incubated with a RBC suspension, KBG and four of five herb medicines constituting KBG provided strong protection for RBC membranes against haemolysis induced by 2,2-azo-bis (2-amidinopropane) dihydrochloride (AAPH), an azo free radical initiator. The inhibitory effect was dose dependent at concentrations of 100-1000 microg/mL. Furthermore, the ingestion of 200 mg of KBG was associated with a significant decrease in susceptibility of RBC to haemolysis in rats.

- 6) Sekiya N. Goto H. Tazawa K. Oida S. Shimada Y. Terasawa K.: **Keishi-bukuryo-gan preserves the endothelium dependent relaxation of thoracic aorta in cholesterol-fed rabbit by limiting superoxide generation.** *Phytotherapy Research*, 16: 524-528, 2002.

Abstract: Formerly, we have reported that keishi-bukuryo-gan prevents the progression of atherosclerosis in cholesterol-fed rabbits and inhibits the free radical-induced RBC haemolysis in rats. The present study was performed to investigate how keishi-bukuryo-gan (KBG) inhibits the early stage of atherosclerosis. Plasma lipid concentration and hydroxyl radical generation during respiratory burst in neutrophils were evaluated at the start and end of the study.

The protective effect of KBG against endothelium disorder due to hypercholesterolaemia was examined. Twelve male Japanese white rabbits (2 kg body weight) were divided into two groups. Group A (n = 6) was fed standard rabbit chow containing 1% cholesterol for 4 weeks. Group B (n = 6) was fed standard rabbit chow containing 1% cholesterol and 1% KBG for 4 weeks. In the plasma lipid concentration, only the lipid peroxide concentration of group A was significantly higher than that of group B. At the end of the study, DMPO-OH, the spin-trapped adduct of hydroxyl radicals generated by neutrophils, was increased in both groups, and this increase was marked in group B. Endothelium-dependent vasodilatation by acetylcholine increased significantly in group B compared with group A. Thus, KBG protects the vascular endothelium function by its antioxidative effect and by inhibiting the release of free radicals from neutrophils in vivo.

7) Kogure T., Mantani N., Goto H., Shimada Y., Tamura J. and Terasawa K.: The effect of interleukin-15 on the expression of killer-cell immunoglobulin-like receptors on peripheral natural killer cells in human. *Mediators of Inflammation*, 11 : 219-224, 2002.

Abstract: Interleukin (IL)-15 has emerged as a key regulator of both natural killer (NK) cell differentiation and activation. The aim of the present study was to investigate the expansion of the population of cells expressing killer-cell immunoglobulin-like receptors (CD158a and CD158b) in human peripheral lymphocytes by treatment with IL-15. One million peripheral lymphocytes were cultured in RPMI1640 medium alone or in medium containing IL-2 at 100 U/ml or IL-15 at 0.1, 1.0, or 10.0 ng/ml for 48 h. After each incubation, we assessed the natural killing activity and the population of CD16(+)CD158a(+)/b(+) cells and CD8(+)CD158a(+)/b(+) cells. IL-15 increased the NK activity and expanded the populations of CD16(+)CD158a(+)/b(+) cells and CD8(+)CD158a(+)/b(+) cells. These actions were dose dependent, and the effects of IL-15 at 1.0 ng/ml were close to those of IL-2 at 100 U/ml. These findings suggest that IL-15 induces the effector functions of resting NK cells throughout the body, and thereby plays a critical role in the activation of tissue-associated immune responses.

8) Shimada Y., Yokoyama Y., Goto H., Sakakibara I., Sekiya N., Mantani N., Sakai S., and Terasawa K.: Protective effect of the hooks and stems of *Uncaria sinensis* against nitric oxide donor-induced neuronal death in cultured cerebellar granule cells. *J. Trad. Med.*, 19 : 15-20, 2002.

Abstract: We have previously shown that an aqueous extract of the hooks and stems of *Uncaria sinensis* (OLIV.) HAVILL., *Uncariae Uncus Cum Ramulus*, protects against glutamate-induced neuronal death in vitro. Nitric oxide (NO) free radicals are also implicated in the process of neuronal death. In this study, we investigated the protective effects of *Uncaria sinensis* extract (USE) and its phenolic and alkaloid fractions against NO donors, sodium nitroprusside (SNP) and 3-morpholinopyridone (SIN-1), -induced neuronal death in cultured rat cerebellar granule cells. MTT assay showed cell viability to be significantly increased by the addition of USE (10, 30 and 100 / μ g/ml) compared with exposure (6, 12 and 24 h) to SNP (30 μ M) only, and by the addition of USE (10 and 30 μ g/ml) compared with exposure (6, 12 and 24 h) to SIN-1 (300 μ M) only. Phenolic fraction of USE (10 and 30 / μ g/ml) significantly protected against SNP (30 / μ M, 24 hr)-induced cell death, and 3 and 10 / μ g/ml of this fraction significantly protected against SIN-1 (300 μ M, 24 hr)-induced cell death. Alkaloid fraction of USE (30 and 100 / μ g/ml) significantly protected against SNP (30 μ M, 24 hr) and SIN-1 (300 μ M, 24 hr)-induced cell death. These results appear to indicate that *Uncaria sinensis* has a protective effect against NO-mediated neuronal death in cultured cerebellar granule cells and that its active components are included in phenolic and alkaloid fractions.

9) Goto H., Shimada Y., Mitsuma T., Shintani T., Nagasaka K., Goto S., Shibahara N. and Terasawa K.: Effect of Keishi-bukuryo-gan on asymptomatic cerebral infarction for short term. *J. Trad. Med.*, 19 : 46-50, 2002.

Abstract: The efficacy of Keishi-bukuryo-gan in patients suffering from asymptomatic cerebral infarction was studied. 142 patients, 32 males and 110 females, with a mean age of 68.9 years, were enrolled and analyzed, and 139 completed the study. They were given Keishi-bukuryo-gan extract (7.5g/day) three times a day for 12 weeks. In comparison to the beginning of the study, Keishi-bukuryo-gan showed improvement with statistical significance in the mean revised version of Hasegawa's dementia scale, Apathy scale and Self-rating depression scale. The number of patients with subjective symptoms as headdullness, headache and dizziness decreased by the treatment with Keishi-bukuryo-gan, and diastolic blood pressure was decreased with statistical significance as compared to the beginning of the study. These results suggest that Keishi-bukuryo-gan is effective against dysfunction of acknowledgment, emotional disorder and subjective symptoms with asymptomatic cerebral infarction.

10) Kasahara Y., Goto H., Shimada Y., Sekiya N., Yang Q. and Terasawa K.: Inhibitory effects of cinnamomi Cortex and cinnamaldehyde on oxygen-derived free radical-induced vasocontraction in isolated aorta of spontaneously hypertensive rats. *J. Trad. Med.*, 19 : 51-57, 2002.

Abstract: We examined the inhibiting effect of Cinnamomi Cortex extract (CCE) and cinnamaldehyde (CA) against vasocontraction induced by oxygen-derived free radicals produced by the xanthine-xanthine oxidase (XOD) system in the thoracic aortic ring of the spontaneously hypertensive rat (SHR), using the organ bath method *in vitro*. The vasocontraction induced by xanthine-XOD in the CCE (10^{-4} g/ml) and CA (10^{-4} M) treatment groups were significantly lower than that in the control group. Further, the amounts of thromboxane B2 (TXB2) produced in the vasocontractive response in the CCE (10^{-4} g/ml) and CA (10^{-4} M) treatment groups were significantly lower than that in the control group. For the purpose of examining the mechanism of the inhibiting effect of CA against thromboxane production, the inhibiting effect of CA against the vasocontraction induced by phospholipase A2 (PLA2) was examined. The vasocontraction induced by PLA2 in the CA (10^{-4} M) treatment group was significantly lower than that in the control group. Moreover, the amount of TXB2 produced by the vasocontractive response in the CA (10^{-4} M) treatment group was significantly lower than that in the control group. From the above findings, it is suggested that Cinnamomi Cortex is an agent which exerts an inhibitory effect on the vasocontractive factor (TXA2) *in vitro*.

11) Shibahara N., Sekiya N., Sakai S., Goto H., Kita T., Shimada Y., Shintani T. and Terasawa K.: Correlation between "oketsu" syndrome and autonomic nervous activity - a diachronic study in the same subjects -. *J. Trad. Med.*, 19 : 81-86, 2002.

Abstract: In order to confirm that the autonomic nervous activity changes with the change in the "oketsu" state using a diachronic study with the same subjects, 20 patients were evaluated by laser Doppler flowmetry and spectral analyses of the R-R intervals (RRs) and systolic blood pressure (SBP). According to the diagnostic criteria of "oketsu", the "oketsu" score (OS) was evaluated. After evaluation of OS and measurement of the parameters, each subject underwent his own Kampo treatment. Twelve weeks later, OS and the parameters were re-evaluated for each subject. The changes in OS and the parameters between week 0 and 12 weeks later were investigated, with the quantity of each change being calculated as Δ . Δ -SBF showed a significant negative correlation with Δ -OS, and Δ -RR-L/H, Δ -SBP-LF and Δ -SBP-L/H revealed significant positive correlations with Δ -OS. It is known that SBF changes with sympathetic nervous activity, and SBP-LF and SBP-L/H reflect a-sympathetic nervous activity. These results suggest that the significant relationship between OS and sympathetic nervous activity was maintained even after change in the "oketsu" state in the same subjects.

12) Mantani N., Sakai S., Kogure T., Goto H., Shibahara N., Kita T., Shimada Y. and Terasawa K.: Herbal medicine and false-positive results on lymphocyte transformation test. *Yakugaku Zasshi - Journal of the Pharmaceutical Society of Japan*, 122(6) : 399-402, 2002.

Abstract: In vitro mitogenic activity of 16 herbs and 3 Kampo (herbal medicine) formulae have been reported in experimental studies. It is not known how many herbs and Kampo formulae in total have mitogenic activity. Lymphocyte transformation test (LTT) is generally utilized to diagnose drug-induced liver injury. In LTT, mitogenic activity is assessed by measuring 3H-thymidine incorporation. The objective of the present study was to determine which herbs and which Kampo formulae caused false-positivity on LTT. We examined 2496 summaries of all admission records from 1979 to 1999 in our department. We selected patients in whom liver injuries were diagnosed as definitely unrelated to Kampo medication. In these patients, LTT was performed for some herbs contained in the suspect Kampo medicines, resulting in positive LTT for 17 herbs: Evodiae Fructus (Goshuyu), Zizyphi Fructus (Taiso), Ginseng Radix (Ninjin), Zingiberis Rhizoma (Shokyo), Hoelen (Bukuryo), Aconiti Tuber (Bushi), Angelicae Radix (Toki), Cnidii Rhizoma (Senkyu), Rehmanniae Radix (Jio), Ephedrae Herba (Mao), Anemarrhenae Rhizoma (Chimo), Cinnamomi Cortex (Keihi), Bupleuri Radix (Saiko), Artemisiae Capillari Spica (Inchinko), Persicae Semen (Tonin), Moutan Cortex (Botanpi) and Paeoniae Radix (Shakuyaku). These results were considered false-positive, because the results were observed in the "definitely unrelated" patients. Mitogenic activity inherent to some herbs and Kampo formulae may sometimes cause false-positivity on LTT in clinical situations. These examples suggest that LTT for Kampo formulae may be unreliable as a diagnostic method for drug-induced liver injury.

13) Rhyu, D.Y., Yokozawa, T., Cho, E.J., Park, J.C.: Prevention of peroxynitrite-induced renal injury through modulation of peroxynitrite production by the Chinese prescription Wen-Pi-Tang. *Free Radical Research*, 36 : 1261-1269, 2002.

Abstract: The effect of Wen-Pi-Tang extract on renal injury induced by peroxynitrite (ONOO⁻) production was investigated using rats subjected to intravenous lipopolysaccharide (LPS) injection and then renal ischemia followed by reperfusion. The plasma level of 3-nitrotyrosine, a marker of cytotoxic ONOO⁻ formation *in vivo*, was enhanced markedly in control rats subjected to LPS plus ischemia-reperfusion, but was significantly reduced by the oral administration of Wen-Pi-Tang extract, at doses of 62.5 and 125 mg/kg body weight/day, for 30 days prior to LPS plus ischemia-reperfusion. The activities of inducible nitric oxide synthase (iNOS) and xanthine oxidase (XOD) in renal tissue of control and Wen-Pi-Tang extract-treated rats did not change significantly, while those of the antioxidant enzymes, superoxide dismutase, catalase and glutathione peroxidase, were significantly increased by the administration of Wen-Pi-Tang extract, indicating that Wen-Pi-Tang improved the defense system by scavenging free radicals, not by directly inhibiting nitric oxide and superoxide production by iNOS and XOD. In addition, the levels of the hydroxylated products, *m*- and *p*-tyrosine, declined, whereas that of phenylalanine increased, after oral administration of Wen-Pi-Tang extract. Furthermore, the elevated plasma urea nitrogen and creatinine levels resulting from LPS plus ischemia-reperfusion process were significantly reduced by Wen-Pi-Tang extract, implying amelioration of renal impairment. The present study indicates that Wen-Pi-Tang extract contributes to the regulation of ONOO⁻ formation and plays a beneficial role against ONOO⁻-induced oxidative injury and renal dysfunction *in vivo*.

14) Yokozawa, T., Kim, H.Y., Cho, E.J.: Erythritol attenuates the diabetic oxidative stress through modulating glucose metabolism and lipid peroxidation in streptozotocin-induced diabetic rats. *J. Agric. Food Chem.*, 50 : 5485-5489, 2002.

Abstract: We investigated the effects of erythritol on rats with streptozotocin- (STZ-) induced diabetes mellitus. Oral administration of erythritol [100, 200, or 400 mg/kg body weight/ day for 10 days] to rats with STZ-induced diabetes resulted in significant decreases in the glucose levels of serum, liver, and kidney. Erythritol also reduced the elevated serum 5-hydroxymethylfurfural level that is glycosylated with protein as an indicator of oxidative stress. In addition, thiobarbituric acid-reactive substance levels of serum and liver and kidney mitochondria were dose-dependently lower in the erythritol-treated groups than in the control diabetic group. Furthermore, the serum creatinine level was reduced by oral administration of erythritol in a dose-dependent manner. These results suggest

that erythritol affects glucose metabolism and reduces lipid peroxidation, thereby improving the damage caused by oxidative stress involved in the pathogenesis of diabetes.

15) Yokozawa, T., Kim, H.Y., Cho, E.J., Choi, J.S.: Antioxidant effects of isorhamnetin 3, 7-di-O- β -D-glucopyranoside isolated from mustard leaf (*Brassica juncea*) in rats with streptozotocin-induced diabetes. *J. Agric. Food Chem.*, 50 : 5490-5495, 2002.

Abstract: To investigate the effects of isorhamnetin 3,7-di-O- β -D-glucopyranoside (isorhamnetin diglucoside), a major flavonoid compound of mustard leaf, on oxidative stress due to diabetes mellitus, *in vivo* and *in vitro* studies were carried out. Oral administration of isorhamnetin diglucoside (10 or 20 mg/kg of body weight/day for 10 days) to rats with streptozotocin-induced diabetes significantly reduced serum levels of glucose and 5-(hydroxymethyl) furfural (5-HMF), which is glycosylated with hemoglobin and is an indicator of oxidative stress. After intraperitoneal administration, isorhamnetin diglucoside did not show these activities. In addition, after oral administration, the thiobarbituric acid-reactive substance levels of serum, and liver and kidney mitochondria declined significantly compared with the control group in a dose-dependent manner, whereas after intraperitoneal administration these levels fell only slightly. On the basis of the oral and intraperitoneal results, it was hypothesized that isorhamnetin diglucoside was converted to its metabolite *in vivo*, and its conversion to its aglycone, isorhamnetin, by β -glucosidase was confirmed; isorhamnetin acted as an antioxidant. Moreover, it was observed that isorhamnetin diglucoside had no effect on the 1,1-diphenyl-2-picrylhydrazyl radical, whereas isorhamnetin showed a potent antioxidant effect *in vitro*. In addition, intraperitoneal administration of isorhamnetin reduced serum glucose and 5-HMF levels. Furthermore, lipid peroxidation in blood, liver, and kidney associated with diabetes mellitus declined after the administration of isorhamnetin. These results suggest that isorhamnetin diglucoside is metabolized *in vivo* by intestinal bacteria to isorhamnetin and that isorhamnetin plays an important role as an antioxidant.

16) Yokozawa, T., Kim, H.Y., Cho, E.J., Choi, J.S.: Protective effects of the BuOH fraction from mustard leaf in a renal ischemia-reperfusion model. *J. Nutr. Sci. Vitaminol.*, 48 : 384-389, 2002.

Abstract: The effect of BuOH fraction from mustard leaf in renal ischemic-reperfused rats was examined. The elevated serum superoxide anion (O_2^-) level and renal xanthine oxidase (XOD) activity in rats subjected to 6 h reperfusion following 1 h ischemia were significantly and dose-dependently declined by the oral administration of BuOH fraction from mustard leaf at doses of 50 and 200 mg/kg body weight/day for 10 days prior to ischemia-reperfusion process. It indicates that BuOH fraction from mustard leaf might scavenge O_2^- or inhibit the generation of O_2^- by XOD activated through the ischemia-reperfusion process. In addition, thiobarbituric acid-reactive substance level in renal mitochondrial fraction was significantly decreased in rats given BuOH fraction orally prior to ischemia-reperfusion in comparison with control rats given vehicle instead of BuOH fraction, implying that a protective action against lipid peroxidation caused by ischemia-reperfusion procedure. Furthermore, oral administration of BuOH fraction lowered the levels of urea nitrogen and creatinine in serum, indicator of renal function. These results suggest that BuOH fraction from mustard leaf has protective effects on ischemia-reperfusion injury playing a role as antioxidant through scavenging O_2^- , inhibiting O_2^- generation by XOD, protecting against lipid peroxidation and improving renal functional impairment.

17) Liu Y., Cao H., Han G., Fushimi H., Komatsu K.: matK and its nucleotide sequencing of crude drug Chuanxiong and phylogenetic relationship between their species from China and Japan. *Acta Pharmaceutica Sinica.*, 37 : 63-68, 2002.

Abstract: AIM: To provide more molecular evidences for species relationship between Chuanxiong (*Ligusticum chuanxiong* Hort.) from China and Japanese Chuanxiong (*Senkyu* in Japanese) (*Cnidium officinale* Makino).

METHODS: To sequence such two genes as internal transcribed spacer (ITS) from nuclear rDNA and maturase for lysine (matK) in tRNA(lys) (UUU) intron from chloroplast DNA of both *Ligusticum chuanxiong* and *Cnidium officinale* using PCR direct sequencing and to analyze the sequence variation of two genes between these two species. **RESULTS:** The matK gene sequence of *Ligusticum chuanxiong* and *Cnidium officinale* is 1268 bp in length, coding 422 amino acids of maturase protein. ITS gene sequence 699 bp, consisting of 54 bp of 18S rRNA-3', 215 bp of ITS1, 162 bp of 5.8S rRNA, 222 bp of ITS2, 46 bp of 26S rRNA-5'. Multiple sequence alignment shows that the sequence of two genes between dried crude drug and fresh voucher material of *Ligusticum chuanxiong* and *Cnidium officinale*, there is 1 variable site (T-->C) in matK (upstream at 595 nt) and ITS (ITS1 at 54 nt) between *Ligusticum chuanxiong* and *Cnidium officinale*. **CONCLUSION:** Based on homology analysis of two genes plastid matK and nuclear ITS, the origin of *Chuanxiong* from China and Japan ought to be identical, the scientific name *Cnidium officinale* of Japanese *Chuanxiong* should be changed to *Ligusticum chuanxiong*.

- 18) 喜多敏明, 後藤博三, 関矢信康, 寺澤捷年: 駆瘀血剤の血清脂質・血液循環に対する影響 (基礎). 産婦人科漢方研究のあゆみ 19: 13-18, 2002.

◇総説 Reviews

- 1) 寺澤捷年, 柴原直利: 漢方の卒前教育カリキュラム. *Geriatric Medicine*, 40: 725-728, 2002.
- 2) 柴原直利: 漢方医学の卒後教育. 漢方と最新治療, 11: 247-252, 2002.
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