民族薬物研究センター　Research Center for Ethnomedicine

薬効解析部　Division of Biofunctional Evaluation

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◇研究目的

民族薬物研究センター薬効解析部は，民族薬物の機能解析に関する研究を推進するために設置された。主な研究内容は以下のとおりであるが，わが国では高齢化や生活習慣病の増加によって疾病構造に大きな変化をきたし，漢方医学の役割や重要性が再認識されてきている。そのためにも基礎的研究を通じて各種疾患，特に慢性疾患に対する漢方薬や個々の生薬，成分の有効性を科学的に実証することが非常に重要な課題であり，これらを中心とした研究を推進している。

◇研究概要

1) 腎疾患における病態の解明と腎臓病治療薬の開発
2) 糖尿病性腎症における漢方方剤のアプローチと分子生物学的解明
3) 加齢 (老化) 及び加齢関連疾患 (いわゆる老年病) の発症機序に対するアンチエイジング産業への開拓
4) 生活習慣病分子標的因子の解明と治療薬の創出
5) 神経回路網形成および神経変性疾患（認知症，脊髄損傷，注意欠陥多動性障害）に関する基礎的研究と，それらに有効な伝統薬物の研究

◇著書

1) 曲曼古麗・阿布力孜, ウイグルの伝統医薬. 横澤隆子編, 1-52, 昭和印刷, 富山, 2007.

◇原著論文

1) **Yamabe N., Kang K.S., Goto E., Tanaka T., and Yokozawa T.: Beneficial Effect of Corni Fructus, a Constituent of Hachimi-jio-gan, on Advanced Glycation End-product-Mediated Renal Injury in Streptozotocin-Treated Diabetic Rats. Biol. Pharm. Bull., 30: 520-526, 2007.**

Abstract: Previous investigations have demonstrated that Hachimi-jio-gan, a Chinese prescription consisting of eight crude drugs, has a therapeutic potential in diabetes and diabetic nephropathy, using these model rats. To add to these findings, we performed this study to assess whether one of the crude drugs, Corni Fructus (*Cornus officinalis* SIEB. et ZUCC.), had an effect on streptozotocin-induced diabetic rats as a major active constituent, compared with an inhibitor of advanced glycation end-product (AGE) formation, aminoguanidine. Diabetic rats were orally administrated Corni Fructus extract (50, 100, 200 mg/kg body weight/d) or aminoguanidine (100 mg/kg body weight/d). Treatment with Corni Fructus for 10 d suppressed hyperglycemia, proteinuria, renal AGE formation, and related protein expressions, *i.e.*, receptor for AGEs, nuclear factor-κB, transforming growth factor-β_1, and N^{ε}-(carboxymethyl)lysine, in the same way as with aminoguanidine. However, improvement of renal function, shown *via* serum creatinine (Cr) and Cr clearance, was superior to aminoguanidine treatment. In conclusion, the present study supported the hypothesis that Corni Fructus plays an important role against diabetic pathogenesis, *i.e.*, reducing glucose toxicities, up-regulating renal function, and consequently ameliorating glycation-associated renal damage; thus, this study may provide a new recognition of crude drugs to clarify the mechanisms of Chinese prescriptions.

2) **Yokozawa T., Kim H.Y., Kim H.J., Okubo T., Chu D.C., and Juneja L.R.: Amla (*Emblica officinalis* Gaertn.) prevents dyslipidaemia and oxidative stress in the ageing process. Br. J. Nutr., 97: 1187-1195, 2007.**

Abstract: Amla (*Emblica officinalis* Gaertn.) is widely used in Indian medicine for the treatment of various diseases. We have investigated the effects of amla on the lipid metabolism and protein expression involved in oxidative stress during the ageing process. SunAmla or ethyl acetate extract of amla, a polyphenol-rich fraction, was administered at a dose of 40 or 10 mg/kg body weight per d for 100 d to young rats aged 2 months and aged rats aged 10 months. The lipid levels, such as cholesterol and TAG, in serum and liver were markedly elevated in aged control rats, while they were significantly decreased by the administration of amla. The PPARα is known to regulate the transcription of genes involved in lipid and cholesterol metabolism. The PPARα protein level in liver was reduced in aged control rats. However, the oral administration of amla significantly increased the hepatic PPARα protein level. In addition, oral administration of amla significantly inhibited the serum and hepatic mitochondrial thiobarbituric acid-reactive substance levels in aged rats. Moreover, the elevated expression level of bax was significantly decreased after the oral administration of amla, while the level of bcl-2 led to a significant increase. Furthermore, the expressions of hepatic NF-κB, inducible NO synthase (iNOS), and cyclo-oxygenase-2 (COX-2) protein levels were also increased with ageing. However, amla extract reduced the iNOS and COX-2 expression levels by inhibiting NF-κB activation in aged rats. These results indicate that amla may prevent age-related hyperlipidaemia through attenuating oxidative stress in the ageing process.

3) **Sasaki S., Tohda C., Kim M., and Yokozawa T.: γ-Aminobutyric Acid Specifically Inhibits Progression of Tubular Fibrosis and Atrophy in Nephrectomized Rats. Biol. Pharm. Bull., 30: 687-691, 2007.**

Abstract: γ-Aminobutyric acid (GABA) was administered orally to rats for 60 days after excision of five-sixths of their kidney volume. A decrease in renal function parameters was observed in these nephrectomized rats. However, the administration of GABA ameliorated renal dysfunction, and a longer administration period of GABA increased its protective effect. In addition, tubular fibrosis was markedly increased at 10 and 60 d in nephrectomized control rats, while GABA administration for 10 d reduced tubular fibrosis to the normal level. Tubular atrophy was markedly induced by nephrectomy, and was significantly reduced by the administration of GABA at 60 d. Furthermore, the nephrectomized control rats exhibited an increased expression level of transforming growth factor-β_1, where GABA significantly decreased it after administration for 10 d. The expression of fibronectin in the tubuli of rats administrated GABA for 60 d was completely and dose-dependently reduced as compared with nephrectomized control rats. However, the improvement effects in glomeruli were less. We also found that $GABA_A$ and $GABA_B$ receptors were specifically localized in tubuli. Specific agonists for $GABA_A$ and $GABA_B$ receptors improved renal function. These results suggest that GABA may have a beneficial effect on renal function in nephrectomized rats by inhibiting fibrosis and atrophy primarily in tubuli, and that it ameliorates losses of renal function in renal failure.

4) **Yokozawa T., Kim Y.A., Kim H.Y., Okamoto T., and Sei Y.: Protective effect of the Chinese prescription Kangen-karyu against high glucose-induced oxidative stress in LLC-PK_1 cells. J. Ethnopharmacol., 109: 113-120, 2007.**

Abstract: We investigated the effects of Chinese prescription Kangen-karyu on high glucose-induced oxidative stress using LLC-PK_1 cells, renal tubular cells, which are the most vulnerable renal tissue to oxidative stress. High-concentration glucose (30mM) treatment induced LLC-PK_1 cell death, but Kangen-karyu, at a concentration of 5, 10 or 50 μg/ml, significantly inhibited high glucose-induced cytotoxicity. In addition, the intracellular reactive oxygen species level was increased by 30mM glucose treatment, but it was concentration-dependently inhibited by Kangen-karyu treatment. Moreover, 30mM glucose treatment induced high levels of superoxide anion, nitric oxide and peroxynitrite. However, Kangen-karyu treatment significantly reduced the radical overproduction induced by high glucose, suggesting Kangen-karyu has radical-scavenging activity that would protect against oxidative stress induced by high glucose. Kangen-karyu also reduced the overexpression of inducible nitric oxide synthase and cyclooxygenase-2 proteins induced by high glucose. Furthermore, treatment with Kangen-karyu, at a concentration of 50 μg/ml, inhibited the nuclear translocation of nuclear factor-kappa B induced by 30mM glucose in LLC-PK_1 cells. These findings indicate that Kangen-karyu is a potential therapeutic agent that will reduce the damage caused by hyperglycemia-induced oxidative stress associated with diabetes.

5) **Rhyu D.Y., Kang K.S., Sekiya M., and Yokozawa T.: Antioxidant Effect of Wen-Pi-Tang and Its Component Crude Drugs on Oxidative Stress. Am. J. Chin. Med., 35: 127-137, 2007.**

Abstract: Oxidative stress plays a key role in the pathophysiologic process of acute and chronic renal diseases. Intracellular component such as lipids, proteins and nucleic acids are easily and rapidly oxidized by excessive reactive oxygen species (ROS), and such reactions lead to increased levels of lipid peroxide. The present study examined the antioxidant effects of Wen-Pi-Tang and its component crude drugs on 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH)- or 2,2'-azobis(2,4-dimethylvaleronitrile) (AMVN)-induced ROS generation and lipid peroxidation of linoleic acid. As a result, Wen-Pi-Tang significantly decreased AAPH or AMVN-induced ROS in renal mitochondrial particles. For the components in Wen-Pi-Tang's prescription, Rhei Rhizoma and Glycyrrhizae Radix extracts strongly inhibited peroxide levels, but Ginseng Radix, Aconiti Tuber and Zingiberis Rhizoma extracts were comparably low. Rhei Rhizoma extract showed the strongest inhibitory activity on oxidative injury, and two of its tannin compounds, (-)-epicatechin 3-*O*-gallate and procyanidin B-2 3,3'-di-*O*-gallate, inhibited AAPH or AMVN-induced ROS significantly. Thus, the present data suggest that Wen-Pi-Tang and its

component crude drugs effectively prevent biological toxicity on oxidative stress through potent antioxidant and anti-lipid peroxidation activities.

6) **Nakagawa T., Goto H., Hikiami H., Yokozawa T., Shibahara N., and Shimada Y.: Protective effects of keishibukuryogan on the kidney of spontaneously diabetic WBN/Kob rats. J. Ethnopharmacol., 110: 311-317, 2007.**

Abstract: Keishibukuryogan, one of the traditional herbal formulations, is used clinically to improve blood circulation. It consists of the following five crude drugs: Cinnamomi Cortex, Poria, Moutan Cortex, Persicae Semen and Paeoniae Radix. In this study, the effects of keishibukuryogan against renal damage in spontaneously diabetic WBN/Kob rats were examined. Oral administration of keishibukuryogan significantly attenuated urinary protein excretion and serum creatinine levels. It did not affect body weight loss and blood glucose levels, but it suppressed renal and hepatic weights of WBN/Kob rats. Keishibukuryogan also reduced fibronectin and transforming growth factor β_1 (TGF-β_1) protein expression in the renal cortex. Furthermore, lipid peroxidation levels in both kidney and liver were significantly lower than those of untreated control WBN/Kob rats. Urinary excretion of 8-hydroxy-deoxyguanosine was suppressed by keishibukuryogan treatment. These results suggest that keishibukuryogan reduces oxidative stress by hyperglycemia, and that it protects renal function and suppresses fibronectin deposition induced by TGF-β_1 production in WBN/Kob rats.

7) **Kang K.S., Kim H.Y., Baek S.H., Yoo H.H., Park J.H., and Yokozawa T.: Study on the Hydroxyl Radical Scavenging Activity Changes of Ginseng and Ginsenoside-Rb_2 by Heat Processing. Biol. Pharm. Bull., 30: 724-728, 2007.**

Abstract: The free radical scavenging activities of *Panax ginseng* C.A. MEYER are known to increase by heat processing. Phenolic acids and Maillard reaction products (MRPs) have been suggested as active free radical scavenging components from our previous research, but heat processing-induced chemical and activity changes of ginsenosides considering the Maillard reaction have not yet been fully elucidated. In this study, we investigated the hydroxyl radical (.OH) scavenging activity changes of ginsengs and ginsenoside-Rb_2 (Rb_2) by heat processing using an electron spin resonance spectrometer. Especially, Rb_2 was heat processed with the same amount of glycine, a frequently used amino acid in the Maillard reaction model system. As a result, the .OH scavenging activities and brown compound levels of ginseng and glycine-Rb_2 mixture were increased by heat processing. However, the increase in .OH scavenging activities were not in accordance with the extents of browning. On the other hand, less-polar ginsenosides such as Rg_3, Rg_5, and Rk_1 were generated from the glycine-Rb_2 mixture by heat processing. The sugar moieties at carbon-20 of Rb_2 were separated by the steaming process, less-polar ginsenosides were produced, and then the separated sugar moieties were thought to form MRPs with glycine. From the .OH scavenging activity tests of Rb_2, glycine, less-polar ginsenosides, and maltol, the increase in .OH scavenging activity was thought to be more closely related to the generation of .OH scavenging ginsenosides such as 20(S)-Rg_3 and Rg_5 by heat processing than MRPs.

8) **Fujii H., Nakagawa T., Nishioka H., Sato E., Hirose A., Ueno Y., Sun B., Yokozawa T., and Nonaka G.: Preparation, Characterization, and Antioxidative Effects of Oligomeric Proanthocyanidin-L- Cysteine Complexes. J. Agric. Food Chem., 55: 1525-1531, 2007.**

Abstract: Controlled acid-catalyzed degradation of proanthocyanidin polymers in grape seeds together with L-cysteine led to oligomeric proanthocyanidin-L-cysteine complexes along with monomeric flavan-3-ol derivatives being isolated, and their structures were confirmed on the basis of spectroscopic data and by chemical means. In addition, comparative studies on the antioxidative and survival effects of oligomeric proanthocyanidin-L-cysteine complexes and proanthocyanidin polymers were performed. The oligomeric proanthocyanidin-L-cysteine complexes showed higher bioavailability and antioxidant capacity and enhanced survival time in the animal test groups. In addition, it is suggested that the

oligomeric complexes may help to prevent oxidative stress and may reduce free radical production.

9) **Kang K.S., Yokozawa T., Yamabe N., Kim H.Y., and Park J.H.: ESR Study on the Structure and Hydroxyl Radical-Scavenging Activity Relationships of Ginsenosides Isolated from *Panax ginseng* C.A. MEYER. Biol. Pharm. Bull., 30: 917-921, 2007.**

Abstract: Ginsenosides have been regarded as the main active components of *Panax ginseng* C. A. MEYER, and the antioxidant activity of ginsenosides *in vivo* is well described. However, there has been virtually no report describing the direct free radical-scavenging activities of ginsenosides through the long history of ginseng research. The hydroxyl radical (.OH)-scavenging activity test using an electron spin resonance spectrometer (ESR) is suggested to be the most appropriate to measure the antioxidant activities of ginsenosides. Therefore, we investigated the .OH-scavenging and ferrous metal ion-chelating activities of several ginsenosides of *Panax ginseng* using ESR for the identification of active ginsenosides and its structure and activity relationships. As a result, 20(*S*)-Rg_3 showed the strongest activity, and the next were in the decreasing order of Rb_1, Rg_1, Rc, Rb_2, and Rd when dissolved with water. The .OH-scavenging activities of ginsenosides were related to the ferrous metal ion-chelating activities of their aglycone, 20(*S*)-protopanaxadiol. In addition, the ferrous metal ion-chelating activities of ginsenosides were thought to be influenced by their types of hydrophilic sugar moieties.

10) **Cho E.J., Yokozawa T., and Okamoto T.: Protective effect of Chinese prescription Kangen-karyu and its crude drug Tanjin against age-related lipidosis in rats. J. Pharm. Pharmacol., 59: 687-694, 2007.**

Abstract: We have investigated the effect of the Chinese prescription Kangen-karyu and its crude drug Tanjin against age-related lipidosis in-vivo in a rat model. The serum and hepatic triglyceride levels were remarkably elevated in 12-month-old compared with two-month-old rats. However, the administration of Kangen-karyu and Tanjin extracts significantly decreased these levels. This suggested a protective role against related pathological conditions as well as hyperlipidaemia. On the other hand, the reduction of the levels of adiponectin in serum with ageing did not show significant changes in rats given diets supplemented with Kangen-karyu and Tanjin extracts. Furthermore, the expression of transcription factors in nuclear hepatic tissue related to lipid metabolism was investigated. The decline in the expression of nuclear peroxisome proliferator-activated receptor α protein in hepatic tissue with age was ameliorated by the administration of Kangen-karyu and Tanjin supplements. On the other hand, the overexpression of sterol regulatory element-binding proteins (SREBP)-1 and SREBP-2 in old rats compared with young rats showed a tendency to decrease with Kangen-karyu and Tanjin administration. The decline of hepatic function with ageing was attenuated by Kangen-karyu and Tanjin, suggesting the beneficial role of Kangen-karyu and Tanjin on lipid metabolism through the improvement of hepatic function. This study has demonstrated that Kangen-karyu and Tanjin inhibited the accumulation of triglyceride with regulation of related protein expressions and they improved hepatic function. Evidence has been provided for the anti-ageing activity of Kangen-karyu and its crude drug Tanjin against age-related lipidosis.

11) **Lee Y.A, Cho E.J., Tanaka T., and Yokozawa T.: Inhibitory Activities of Proanthocyanidins from Persimmon against Oxidative Stress and Digestive Enzymes Related to Diabetes. J. Nutr. Sci. Vitaminol., 53: 287-292, 2007.**

Abstract: The present study was carried out to evaluate the promising potential of polymers and oligomers from proanthocyanidins of persimmon peel as antioxidants and therapeutic agents for diabetes. Both polymers and oligomers showed the scavenging effect of 2,2-diphenyl-l-picrylhydrazyl, with IC_{50} values of 4.35 and 2.41 μg/mL, respectively, and they also showed a protective activity against protein oxidation induced by 2,2'-azobis (2-amidinopropane) dihydrochloride. In particular, oligomers exerted a stronger activity against free radicals than polymers. In addition, to investigate their protective potential against diabetes-related pathological conditions, their inhibitory activities on digestive enzymes and advanced

glycation endproduct (AGE) formation were evaluated. Polymers showed a strong inhibitory activity against α-amylase, while oligomers had a relatively weak effect. This suggests that the inhibition of α-amylase activity would probably depend on the degree of polymerization. On the other hand, against α-glucosidase activity and AGE formation, oligomers exerted a stronger protective effect than polymers. The present study suggests that polymers and oligomers from proanthocyanidins of persimmon peel could play a role as antidiabetic agents with antioxidative effects. Moreover, oligomers rather than polymers from proanthocyanidins of persimmon peel may be expected to be a more promising antioxidative and antidiabetic agent in relation to utilization in biological systems.

12) **Yamabe N., and Yokozawa T.: Protective effect of Hachimi-jio-gan against the development of pancreatic fibrosis and oxidative damage in Otsuka Long-Evans Tokushima Fatty rats. J. Ethnopharmacol., 113: 91-99, 2007.**

Abstract: In our previous study, the polyherbal drug Hachimi-jio-gan was reported to possess a protective effect against the progression of diabetic nephropathy by attenuating glucose toxicity and renal damage with a type 2 diabetic model, Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Based on these findings, this study was undertaken to reveal the effect of Hachimi-jio-gan on pancreatic damage focusing on fibrosis and oxidative stress in type 2 diabetes. OLETF rats were orally administered Hachimi-jio-gan for 32 weeks, and we assessed the changes in the serum glucose level every 8 weeks, as well as those of body weight, and food and water consumption every 4 weeks. In addition, pancreatic wet weight, insulin content, and Western blot analyses of transforming growth factor-β_1, fibronectin, and nuclear factor-κB-related inflammatory enzymes, such as inducible nitric oxide synthesis and cyclooxygenase-2, were also performed in the pancreas. As a consequence, long-term treatment with Hachimi-jio-gan had a hypoglycemic effect, reducing pancreatic atrophy and fibrosis, and ameliorating the oxidative status. Therefore, this may provide evidence that Hachimi-jio-gan is a therapeutic target for preventing the development of pancreatic damage concomitant with hyperglycemia in type 2 diabetes.

13) **Yokozawa T., Kim Y.A., Kim H.Y., Lee Y.A, and Nonaka G.: Protective effect of persimmon peel polyphenol against high glucose-induced oxidative stress in LLC-PK$_1$ cells. Food Chem. Toxicol., 45: 1979-1987, 2007.**

Abstract: The effect of persimmon peel polyphenol (PPP) on high glucose-induced oxidative stress was investigated using LLC-PK$_1$ cells, which is susceptible to oxidative stress. High-concentration glucose (30 mM) treatment induced LLC-PK$_1$ cell death, but high molecular-PPP (HMPPP) and low molecular-PPP (LMPPP), at concentrations of 5 or 10 μg/ml, significantly inhibited the high glucose-induced cytotoxicity. Furthermore, treatment with HMPPP or LMPPP dose-dependently reduced the intracellular reactive oxygen species level increased by 30 mM glucose. In addition, nitric oxide, superoxide and peroxynitrite levels were increased by 30 mM glucose treatment, but they were concentration-dependently inhibited by HMPPP or LMPPP treatment. High glucose levels induced the overexpressions of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) proteins, but HMPPP or LMPPP treatment reduced the overexpressions of these proteins. HMPPP or LMPPP also inhibited the nuclear translocation of nuclear factor-kappa B (NF-κB) induced by 30 mM glucose in LLC-PK$_1$ cells. In particular, LMPPP exhibited stronger inhibitory activities on high glucose induced oxidative stress than HMPPP. These findings indicate the potential benefits of persimmon peel as a valuable source of antioxidants in the diabetic condition which will reduce the oxidative stress induced by hyperglycemia.

14) **Yamabe N., Kang K.S., Matsuo Y., Tanaka T., and Yokozawa T.: Identification of Antidiabetic Effect of Iridoid Glycosides and Low Molecular Weight Polyphenol Fractions of Corni Fructus, a Constituent of Hachimi-jio-gan, in Streptozotocin-Induced Diabetic Rats. Biol. Pharm. Bull., 30: 1289-1296, 2007.**

Abstract: In our previous study, Corni Fructus (*Cornus officinalis* SIEB. et ZUCC.), a component crude

drug of the Chinese prescription Hachimi-jio-gan, was reported to reduce glucotoxicities, up-regulate renal function, and consequently ameliorate glycation-associated renal damage as well as Hachimi-jio-gan. Based upon these facts, we prepared Corni Fructus fractions and evaluated which fraction contained the effective components against diabetes, using one iridoid glycoside and three polyphenol fractions, which were expected to possess stronger activities than Corni Fructus, administered orally at a dose of 20 mg/kg body weight/d for 10 d, respectively. As a result, iridoid glycosides and low molecular weight polyphenol fractions could reduce the pathogenesis of diabetic renal damage, each having different mechanisms, *i.e.*, iridoid glycosides successfully decreased the hyperglycemic state and affected renal advanced glycation end-product (AGE) accumulation, such as N^{ε}-(carboxyethyl)lysine and N^{ε}-(carboxymethyl)lysine, while low molecular weight polyphenol fractions could reduce renal lipid peroxidation, the receptor for AGE, and inducible nitric oxide synthase. Overall, these data suggest that iridoid glycosides and low molecular weight polyphenols purified from Corni Fructus improve metabolic parameters associated with the development of diabetic renal damage. The main active components of these fractions are discussed.

15) Kang K.S., Yamabe N., Kim H.Y., Okamoto T., Sei Y., and Yokozawa T.: Increase in the free radical scavenging activities of American ginseng by heat processing and its safety evaluation. J. Ethnopharmacol., 113: 225-232, 2007.

Abstract: We previously reported the increase in free radical scavenging activities of Korean ginseng (KG, *Panax ginseng* C.A. Meyer) by heat processing. In the United States, American ginseng (AG, *Panax quinquefolium* L.) is a more commonly used herbal medicine than KG, but heat processing-induced chemical and activity changes of AG are not well known. Therefore, we compared the changes in ginsenosides, total phenolic contents, Maillard reaction product (MRP) levels, and several free radical scavenging activities of AG by heat processing. In addition, a short-term toxicity assessment in rats was also conducted for the identification of certain toxic effects of AG after heat processing. As a result, the ginsenosides were deglycosylated at carbon-20 and their total contents were lowered, but the total phenolic contents and MRP levels of AG were about 2.5 and 9.3 times increased, respectively, by heat processing. In addition, all free radical scavenging activities of AG were significantly increased by heat processing. Moreover, there were no toxic signs or decreases in renal and hepatic function parameters of rats administered heat-processed AG. Therefore, heat processing, as in KG, is a useful method to enhance the free radical scavenging activities of AG by the increases in total phenolic contents and MRP levels.

16) Yokozawa T., Kim H.J., Yamabe N., Okamoto T., and Cho E.J.: The protective role of Kangen-karyu against fructose-induced metabolic syndrome in a rat model. J. Pharm. Pharmacol., 59: 1271-1278, 2007.

Abstract: The protective effect of Kangen-karyu extract and its mechanisms against fructose-induced metabolic syndrome have been investigated using a rat model. Male Wistar rats were fed a high fructose (65%) diet or standard chow for one week, and for two subsequent weeks were treated with 50 or 100 mg kg^{-1} body weight/day Kangen-karyu extract or vehicle. Serum glucose, glycosylated protein, triglyceride (TG), total cholesterol, and blood pressure levels of high-fructose-fed rats were increased compared with those of normal rats. However, Kangen-karyu extract ameliorated the high-fructose-induced metabolic syndrome including hyperglycaemia and hypertriglyceridaemia. In addition, the increase of hepatic TG content in rats given the high fructose diet was significantly inhibited with the regulation of sterol regulatory element-binding protein (SREBP)-1 expression by Kangen-karyu extract. On the other hand, peroxisome proliferator-activated receptor α and SREBP-2 protein levels were not affected by the feeding of the high fructose diet or Kangen-karyu extract. Moreover, Kangen-karyu extract administration to high-fructose-fed rats markedly reduced the thiobarbituric acid-reactive substance levels in serum, hepatic homogenate, and mitochondria. Furthermore, it inhibited the increase of cyclooxygenase (COX)-2 with

the regulation of nuclear factor-kappa B (NF-κB) and bcl-2 proteins in the liver, suggesting that the protective potential of Kangenkaryu extract against metabolic syndrome would be attributed to the regulation of COX-2, NF-κB, and bcl-2 signalling pathways. This study indicated that Kangen-karyu extract significantly improved high-fructose-induced metabolic syndrome such as hyperglycaemia, hyperlipidaemia, and hypertension through the reductions of TG and cholesterol contents with the regulation of hepatic SREBP-1 protein and the NF-κB signalling pathway.

17) **Kitani K., Osawa T., and Yokozawa T.: The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. Biogerontology, 8: 567-573, 2007.**

Abstract: The effect of feeding of two different antioxidants, tetrahydrocurcumin (TC) and green tea polyphenols (PPs) on the survival of male C57BL/6 mice was examined. Mice that started to receive diets containing TC (0.2%) at the age of 13 months had significantly longer average life spans (days, mean ± SD) than control mice (797.6 ± 151.2 vs. 882 ± 154.6, both n = 50, controls vs. TC treated, plus 11.7%, $P < 0.01$). The 10% longest survival was also significantly greater in TC-treated mice (plus 6.5%, $P < 0.01$). In contrast, in mice that started to receive TC in their 19th month of life, no significant difference from the control mice was found for either the average life span or the 10% longest survival. In mice that received water containing PPs (80 mg/l), the average life span was also significantly longer than in the control mice (801 ± 121.5 vs. 852.7 ± 88.2, plus 6.4%, $P < 0.05$), although the 10% longest survival was not significantly different from that in the control mice ($P > 0.05$). The body weights of the TC (but not PP) fed mice, were slightly (2-4%) but significantly ($P < 0.05$) lower than the values for the corresponding ages in the control mice in the first six months of treatment. Thereafter, the difference in average body weight between the control and the TC-fed animals was totally lost. Although an additional contribution of an unintended slight decrease in food intake due to TC feeding (suspected due to the difference in body weight) is not excluded, we suggest that the feeding of nutritional antioxidants such as TC and PPs may have the potential to beneficially modify the life spans of animals.

18) **Yokozawa T., Kim H.Y., Kim H.J., Tanaka T., Sugino H., Okubo T., Chu D.C., and Juneja L.R.: Amla (*Emblica officinalis* Gaertn.) Attenuates Age-Related Renal Dysfunction by Oxidative Stress. J. Agric. Food Chem., 55: 7744-7752, 2007.**

Abstract: To investigate the effects of amla on renal dysfunction involved in oxidative stress during the aging process, we employed young (2 months old) and aged (13 months old) male rats and administered SunAmla (Taiyo Kagaku Co., Ltd., Japan) or an ethyl acetate (EtOAc) extract of amla, a polyphenol-rich fraction, at a dose of 40 or 10 mg/kg body weight/day for 100 days. The administration of SunAmla or EtOAc extract of amla reduced the elevated levels of serum creatinine and urea nitrogen in the aged rats. In addition, the tail arterial blood pressure was markedly elevated in aged control rats as compared with young rats, while the systolic blood pressure was significantly decreased by the administration of SunAmla or EtOAc extract of amla. Furthermore, the oral administration of SunAmla or EtOAc extract of amla significantly reduced thiobarbituric acid-reactive substance levels of serum, renal homogenate, and mitochondria in aged rats, suggesting that amla would ameliorate oxidative stress under aging. The increases of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 expression in the aorta of aging rats were also significantly suppressed by SunAmla extract or EtOAc extract of amla, respectively. Moreover, the elevated expression level of bax, a proapoptotic protein, was significantly decreased after oral administration of SunAmla or EtOAc extract of amla. However, the level of bcl-2, an antiapoptotic protein, did not show any difference among the groups. The expressions of renal nuclear factor-κB (NF-κB), inhibitory κB in cytoplasm, iNOS, and COX-2 protein levels were also increased with aging. However, SunAmla or EtOAc extract of amla reduced the iNOS and COX-2 expression levels by inhibiting NF-κB activation in the aged rats. These results indicate that amla would be a very useful antioxidant for the prevention of age-related renal disease.

19) **Kang K.S., Kim H.Y., Yamabe N., Park J.H., and Yokozawa T.: Preventive effect of 20(*S*)-ginsenoside Rg_3 against lipopolysaccharide-induced hepatic and renal injury in rats. Free Radic. Res., 41: 1181-1188, 2007.**

Abstract: The preventive effect of 20(*S*)-ginsenoside Rg_3 (20(*S*)-Rg_3) on lipopolysaccharide (LPS)-induced oxidative tissue injury in rats was investigated in this study. The elevated serum nitrite/nitrate, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and creatinine levels in LPS-treated control rats were significantly decreased following 15 consecutive days of 20(*S*)-Rg_3 administration. In addition, thiobarbituric acid-reactive substance levels in the serum, liver and kidney were dose-dependently lower in 20(*S*)-Rg_3-treated groups than in the LPS-treated control group. The nuclear factor-κB (NF-κB), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and heme oxygenase-1 (HO-1) protein expressions in the liver and kidney were significantly increased by LPS treatment. However, the 20(*S*)-Rg_3 administrations significantly decreased these protein expressions except for HO-1 in the liver. On the other hand, in the kidney, oral administration of 20(*S*)-Rg_3 showed a tendency to reduce NF-κB and iNOS protein expressions and also significantly reduced the elevated COX-2 and HO-1 protein expressions at a dose of 10 mg/kg body weight/day. All these results suggest the preventive effect of 20(*S*)-Rg_3 against LPS-induced acute oxidative damage in the liver and kidney and the preventive effect of 20(*S*)-Rg_3 administration against LPS toxicity was thought to be more predominant in the liver than kidney.

20) **Kang K.S., Lee Y.J., Park J.H., and Yokozawa T.: The Effects of Glycine and L-Arginine on Heat Stability of Ginsenoside Rb_1. Biol. Pharm. Bull., 30: 1975-1978, 2007.**

Abstract: To identify the effects of amino acids on the heat stability of ginsenoside Rb_1 (Rb_1, Rb_1 was heat-processed at 120°C with or without glycine or L-arginine. Rb_1 was changed into 20(*S*)-Rg_3, 20(*R*)-Rg_3, Rk_1, and Rg_5 by heat-processing through glycosyl elimination and epimerization of carbon-20 by SN1 reaction. Similarly, Rb_1 was changed into 20(*S*)-Rg_3, 20(*R*)-Rg_3, Rk_1, and Rg_5 when it was heat-processed with the same amount of glycine, but the generated amount of 20(*S*)-Rg_3 was higher than when Rb_1 was heat-processed without amino acids, and a significant increase in Maillard reaction products (MRPs) was noted. On the other hand, there were no structural changes in Rb_1 and the generation of MRPs when Rb_1 was heat-processed with the same amount of L-arginine. The improved heat stability of Rb_1 brought about by the addition of L-arginine was thought to be closely related to its characteristics of interfering with nonenzymatic glycation and forming hydrogen bonds with Rb_1.

21) **Yokozawa T., and Kim Y.J.: Piceatannol Inhibits Melanogenesis by Its Antioxidative Actions. Biol. Pharm. Bull., 30: 2007-2011, 2007.**

Abstract: In our efforts to find new skin lightening agents, piceatannol (PICE) was investigated for its antioxidative property and ability to inhibit melanogenesis. In this study, PICE's effect on inhibition of mushroom tyrosinase, and tyrosinase inhibiting activity and melanin content were assessed utilizing the B16F10 melanoma cell (B16 cell) culture system. Results indicated that PICE has a strong antityrosinase activity (IC_{50}=1.53 μM). To evaluate the relative efficacy of PICE compared to other tyrosinase inhibitors, its inhibitory effect was compared and showed that PICE was significantly stronger than kojic acid (IC_{50}=50.1 μM) and resveratrol (IC_{50}=63.2 μM). Furthermore, PICE was shown to down-regulate melanin content. To document PICE's antioxidative property, which is known to influence melanogenic activity, we assessed reactive species (RS) generation, reduced glutathione (GSH) and oxidized glutathione (GSSG) levels in these B16 cells. The results showed that PICE suppressed RS generation and enhanced the GSH/GSSG ratio. In conclusion, our results indicated that the antimelanogenic action of PICE is likely exhibited by the combined effect of PICE's antioxidative property and its ability to suppress RS generation while increasing the GSH/GSSG ratio.

22) **Kim H.Y., Kang K.S., Yamabe N., Nagai R., and Yokozawa T.: Protective Effect of Heat-Processed American Ginseng against Diabetic Renal Damage in Rats. J. Agric. Food Chem., 55: 8491-8497, 2007.**

Abstract: We investigated the effects of American ginseng (AG) and heat-processed American ginseng (H-AG) on diabetic renal damage using streptozotocin (STZ)-induced diabetic rats in this study. The diabetic rats showed a loss of body weight gain, and increases in kidney weight, food intake, water intake, and urine volume, whereas the oral administration of H-AG at a dose of 100 mg/kg of body weight per day for 20 days attenuated these diabetes-induced physiological abnormalities. Among the renal function parameters, the elevated urinary protein levels in diabetic control rats were significantly decreased by the AG or H-AG administrations, and the decreased creatinine clearance level was significantly increased in H-AG-administered rats. In addition, the markedly high serum levels of glucose and glycosylated protein in diabetic control rats were significantly decreased by the administration of H-AG, implying that H-AG might prevent the pathogenesis of diabetic complications caused by impaired glucose metabolism and glycosylation of serum proteins. Although no significant ameliorations were shown in overexpressed protein expressions related to diabetic oxidative stress by the AG or H-AG administrations, the accumulation of N^{ε}-(carboxymethyl)lysine and receptors for advanced glycation endproduct (AGE) expressions were significantly reduced by the administration of H-AG. On the basis of these results, we found that AG and H-AG inhibit AGE accumulation in diabetic rat kidney by their hypoglycemic and renal function ameliorating effects, and this effect was stronger in the H-AG-administered group than in the AG-administered group. These findings indicate that H-AG may have beneficial effect on pathological conditions associated with diabetic nephropathy.

23) **Kang K.S., Yamabe N., Kim H.Y., and Yokozawa T.: Effect of sun ginseng methanol extract on lipopolysaccharide-induced liver injury in rats. Phytomedicine, 14: 840-845, 2007.**

Abstract: Sun ginseng (SG) is heat-processed *Panax ginseng* C.A. MEYER steamed at 120°C, which has ginsenoside-Rg_3, -Rk_1, and –Rg_5 as its main ginsenoside components. The effect of SG on lipopolysaccharide (LPS)-induced liver injury in rats was investigated in this study. Intravenous injection of LPS induced excessive nitric oxide (.NO) generation in serum and increased the hepatic mitochondrial thiobarbituric acid-reactive substance (TBA-RS) level. However, the elevated TBA-RS level was significantly lowered by 15 consecutive days of SG administrations. In addition, up-regulated hepatic inducible nitric oxide synthase and heme oxygenase 1 levels in LPS-treated control rats were significantly lowered and increased, respectively, by 100 mg/kg body weight/day of SG administration. These antioxidant effects were thought to be partially related to the deactivation of nuclear factor-κB by SG administration.

24) **Lee Y.A, Kim Y.J., Cho E.J., and Yokozawa T.: Ameliorative Effects of Proanthocyanidin on Oxidative Stress and Inflammation in Streptozotocin-Induced Diabetic Rats. J. Agric. Food Chem., 55: 9395-9400, 2007.**

Abstract: Recent evidence strongly suggests that oxidative stress due to redox imbalance is causally associated with inflammatory processes and various diseases including diabetes. We examined the effects of proanthocyanidin from persimmon peel, using both oligomers and polymers, against oxidative stress with elucidation of the underlying mechanisms in streptozotocin-induced diabetic rats. The elevation of lipid peroxidation in the kidney and serum under the diabetic condition was decreased by the administration of proanthocyanidin. The suppression of reactive oxygen species generation and elevation of the reduced glutathione/oxidized glutathione ratio were observed in the groups administered proanthocyanidin. These results support the protective role of proanthocyanidin from oxidative stress induced by diabetes. Moreover, proanthocyanidin, especially its oligomeric form, affected the inflammatory process with regulation of related protein expression, inducible nitric oxide synthase,

cyclooxygenase-2, and upstream regulators, nuclear factor κB, and inhibitor-binding protein κB-alpha. Proanthocyanidin ameliorated the diabetic condition by decreases of serum glucose, glycosylated protein, serum urea nitrogen, urinary protein, and renal advanced glycation endproducts. In particular, oligomeric proanthocyanidin exerted a stronger protective activity than the polymeric form. This suggests that the polymerization of proanthocyanidin has an effect on its protective effect against diabetes. The present study supports the beneficial effect of proanthocyanidin against diabetes and oxidative stress-related inflammatory processes.

25) **Kim S.E., Rhyu D.Y., Yokozawa T., and Park J.C.: Antioxidant Effect of *Alisma plantago-aquatica* var. *orientale* and Its Main Component. Kor. J. Pharmacogn., 38: 372-375, 2007.**

Abstract: Reactive oxygen species(ROS) or free radicals are produced in the pathogenesis of human diseases including atherosclerosis, diabetes, cancer, and aging. Antioxidants are associated with the prevention of ROS-induced tissue and cellular damage in the various diseases. This study investigated the antioxidative activities of the methanol extract of *Alisma plantagoaquatica var. orientale* and its main component under conditions of radical generation using allophycocyanin and ferric-thiocyanate assay. Alisol B 23-acetate as a main component was isolated from the methanol extract of *Alisma plantago-aquatica var. orientale.* In results, the extract of *Alisma plantago-aquatica var. orientale* showed inhibitory activity on AAPH [2,2'-azobis(2-amidinopropane)dihydrochloride]-induced protein oxidation. Also, the extract of *Alisma plantago-aquatica var. orientale* and alisol B 23-acetate inhibited lipid peroxidation. These results indicate that *Alisma plantago-aquatica var. orientale* and alisol B 23-acetate show promise as therapeutic agents for various damages involving free radical reactions.

26) **Sekiya M., Kashiwada Y., Nabekura T., Kitagawa S., Yamagishi T., Yokozawa T., Ichiyanagi T., Ikeshiro Y., and Takaishi Y.: Effect of Triterpenoids Isolated from the Floral Spikes of *Betula platyphylla* var. *japonica* on P-Glycoprotein Function. Planta Med., 73: 1558-1562, 2007.**

Abstract: One of the major causes of multidrug resistance (MDR) in cancer cells is over-expression of P-glycoprotein (P-gp). We studied the effects of 20 triterpenes isolated from the floral spikes of *Betula platyphylla* var. *japonica* (*B. platyphylla*) on P-gp function based on our previous finding that some of them showed MDR reversing effects. We evaluated accumulations and effluxes of rhodamine 123 as a P-gp substrate with P-gp over-expressing KB-C2 cells. Among the 20 triterpenes, compounds **3**, **4**, **8**, **9**, **13**, **15**, and **20** increased rhodamine 123 accumulations in KB-C2 cells, and three (**8**, **13**, and **20**) of them also inhibited efflux of rhodamine 123 out of cells. In addition, compounds **13** and **20** showed a weak inhibitory activity of P-gp ATPase. These results suggested that MDR reversing effects of compounds **13** and **20** are partly involved in inhibition of P-gp ATPase.

27) **Tohda C., Nakanishi R., and Kadowaki M.: Learning-deficits and agenesis of synapses and myelinated axons in phosphoinositide-3 kinase-deficient mice. Neurosignals, 15: 293-306, 2007.**

Abstract: Although previous studies have reported a role for phosphoinositide-3 kinase (PI3K) in axonal definition and growth in vitro, it is not clear whether PI3K regulates axonal formation and synaptogenesis in vivo. The goal of the present study was to clarify the role of PI3K in behavioral functions and some underlying neuroanatomical structures. Immunohistochemistry, an electron-microscopic analysis and behavioral tests were carried out. Knockout mice lacking the p85alpha regulatory subunit of PI3K (p85alpha-/- mice) significantly showed learning deficits, restlessness and motivation deficit. Expression of phosphorylated Akt, which indirectly shows the activity of PI3K, was high in myelinated axons, especially in axonal bundles in the striatum of wild-type mice, but was significantly low in the striatum, cerebral cortex and the hippocampal CA3 of p85alpha-/- mice. The axonal marker protein level decreased

mainly in the striatum and cerebral cortex of p85alpha-/- mice. In these two regions, myelinated axons are rich in the wild-type mice. However, the density of myelinated axons and myelin thickness were significantly low in the striatum and cerebral cortex of p85alpha-/- mice. Synaptic protein level was clearly decreased in the striatum, cerebral cortex, and hippocampus of p85alpha-/- mice when compared with wild mice. The present results suggest that PI3K plays a role in the generation and/or maintenance of synapses and myelinated axons in the brain and that deficiencies in PI3K activity result in abnormalities in several neuronal functions, including learning, restlessness and motivation.

28) **Nakayama N., and Tohda C.: Withanoside IV improves hindlimb function by facilitating axonal regrowth and increase in peripheral nervous system myelin level after spinal cord injury. Neurosci. Res., 58: 176-182, 2007.**

Abstract: Although methylprednisolone is the clinically standard medication and almost the only therapy for spinal cord injury (SCI), its effect on functional recovery remains questionable. Transplantation strategies using sources such as neural stem cells and embryonic spinal cord still have some hurdles to overcome before practical applications become available. We therefore aimed to develop a practical medication for SCI. Per oral treatment with withanoside IV, which was previously shown to regenerate neuronal networks in the brain, improved locomotor functions in mice with SCI. In the spinal cord after SCI, axons were crushed in the white matter and gray matter, and central nervous system (CNS) myelin level decreased. In mice treated with withanoside IV (10micromol/kg body weight/day, for 21 days), axonal density and peripheral nervous system (PNS) myelin level increased. The loss of CNS myelin and increase in reactive gliosis were not affected by withanoside IV. These results suggest that oral administration of withanoside IV may ameliorate locomotor functions by facilitating both axonal regrowth and increase in PNS myelin level.

◇総　説

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3) 小松かつ子, 佐々木陽平, 東田千尋, 田中 謙：鬱金類生薬の基原と品質. Foods & Food Ingredients Journal of Japan, 212: 345-356, 2007.

◇学会報告　(*: 特別講演，シンポジウム，ワークショップ等)

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3) 姜 奇成, 山辺典子, 金 賢栄, 横澤隆子：Lipopolysaccharide 誘発肝障害モデルに対する加熱修治した薬用人参の保護効果. 日本薬学会第 127 年会, 2007, 3, 28–30, 富山.
4) 姜 奇成, 金 賢栄, 白 承勲, 朴 政一, 横澤隆子：ジンセノサイド Rb_2 とグリシンの加熱修治による構造の変化とヒドロキシルラジカル消去活性. 日本薬学会第 127 年会, 2007, 3, 28–30, 富山.
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* 10) 東田千尋：Neuron の極性形成を促進させる multiple molecular mechanism により神経変性疾患を治療する和漢薬 (シンポジウム). 日本薬学会第 127 年会, 2007, 3, 28–30, 富山.

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14) 佐々木澄代, 横澤隆子：γ-Aminobutyric acid (GABA) による線維化抑制と作用点の探索. 第 50 回日本腎臓学会学術総会, 2007, 5, 17–20, 浜松.

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◇共同研究

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2) 青柳一正：筑波技術大学, 田中 隆：長崎大学薬学部, 柏田良樹：新潟薬科大学薬学部, 金 賢栄：ソウル大学薬学部, 永井竜児：熊本大学病態生化学, 野中源一郎：ウサイエン製薬(株)「抗酸化に関する研究」
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4) 根本英雄：富山大学,「withanolide 類の研究」「新規化合物の神経保護作用の研究」

◇研究費取得状況

1) 文部科学省科学研究費, 基盤研究 C (代表：横澤隆子)「柿ポリフェノールオリゴマーの製造技術の確立と抗加齢機能性食品の開発」
2) 経済産業省「地域新生コンソーシアム研究開発事業」(分担：横澤隆子)「柿ポリフェノールオリゴマーを用いた抗加齢機能製品の開発」
3) つくし奨学・研究基金 (代表：横澤隆子)「糖尿病性腎症に対する漢方方剤治療の基礎的研究」
4) 文部科学省研究費, 基盤研究 C (代表：東田千尋)「新規の抗痴呆薬となる withanolide 類を用いたシナプス形成機序の解明」
5) 文部科学省研究費, 基盤研究 B (分担：東田千尋)「アジアにおける漢薬資源の調査と薬用植物の多様性の解析」
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博士論文：

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