

The actions of various prescriptions on rats with experimental renal failure

Takako YOKOZAWA,* Zun Li MO, Xiao Qi WU and Hikokichi OURA

*Department of Applied Biochemistry, Research Institute for Wakan-Yaku,
Toyama Medical and Pharmaceutical University**(Received October 19, 1987. Accepted November 16, 1987.)*

Abstract

Seven prescriptions containing rhubarb and prescriptions used for renal diseases were selected to examine their actions on rats with renal failure. As a result of administration, serum levels of urea nitrogen (group given a 60-mg dose), creatinine (groups given 30- and 60-mg doses), methylguanidine, guanidinosuccinic acid (groups given doses of 15, 30, and 60 mg) and inorganic phosphate (group given a 60-mg dose) were significantly lowered, while an improvement in calcium value was found in the group given a 60-mg dose of Daiô-busi-tô (Da-Huang-Fu-Zi-Tang). Tôkaku-Zyôki-tô (Tao-He-Cheng-Qi-Tang) produced significant reductions in urea nitrogen, creatinine, methylguanidine, guanidinosuccinic acid and inorganic phosphate, and a significant increase in calcium in the group given a minimum dose of 12.5 mg. San'ô-syasin-tô (San-Huang-Xie-Xin-Tang) did not produce any significant changes except for lowered methylguanidine. Both Hatimi-ziô-gan (Ba-Wei-Di-Huang-Wan) (urea nitrogen, creatinine, and methylguanidine) and Simotu-tô (Si-Wu-Tang) (urea nitrogen and guanidinosuccinic acid) showed significant lowering actions when administered at the largest dose of 50 mg. By contrast, methylguanidine was increased and no improvement of uremia was found following the use of Syô-saiko-tô (Xiao-Chai-Hu-Tang). Sairei-tô (Chai-Ling-Tang) significantly increased the levels of urea nitrogen, creatinine and methylguanidine, and showed a tendency to aggravate uremia.

Key words renal failure, Daiô-busi-tô, Tôkaku-zyôki-tô, Hatimi-ziô-gan, uremia, rat

Abbreviations Daiô-busi-tô (Da-Huang-Fu-Zi-Tang), 大黃附子湯; Hatimi-ziô-gan (Ba-Wei-Di-Huang-Wan), 八味地黃丸; Onpi-tô (Wen-Pi-Tang), 溫脾湯; Sairei-tô (Chai-Ling-Tang), 柴苓湯; San'ô-syasin-tô (San-Huang-Xie-Xin-Tang), 三黃瀉心湯; Simotu-tô (Si-Wu-Tang), 四物湯; Syô-saiko-tô (Xiao-Chai-Hu-Tang), 小柴胡湯; Tôkaku-zyôki-tô (Tao-He-Cheng-Qi-Tang), 桃核承氣湯

Introduction

Conservative treatment (dietetics and medicinal therapy) is a widely practiced remedy for chronic renal failure. The present authors have been examining the action of crude drugs on rats with experimental renal failure as an approach to developing an effective medicinal therapy. These studies have revealed that the traditional Chinese prescription "Onpi-tô (Wen-Pi-Tang)" composed of Rhei Rhizoma, Ginseng Radix, Gly-

cyrrhizae Radix, Zingiberis Rhizoma, and Aconiti Tuber is chiefly effective for delaying the progress of renal failure by inhibiting the production of methylguanidine, which is known to be a potent uremic toxin, and improving various forms of metabolic and hormonal abnormalities.¹⁻⁶⁾ A recently published case report has revealed that patients with chronic renal failure respond well to Onpi-tô.^{7,8)} In the present study, seven varieties of prescriptions containing rhubarb and prescriptions used for treating renal diseases were selected in order to search for effective prescriptions

*〒 930-01 富山市杉谷 2630
富山医科薬科大学和漢薬研究所臨床利用部門 横澤隆子
Sugitani, Toyama 930-01, Japan

other than Onpi-tô by examining their action in rats with adenine-induced chronic renal failure in terms of their effects on urea nitrogen, creatinine, guanidino compounds, and electrolytes in serum.

Materials and Methods

Animals and treatment : Male rats of the JCL : Wistar strain with a body weight of about 150 g, were kept in an animal room at an ambient temperature of $22 \pm 1^\circ\text{C}$ and with lights on from 6 a.m. to 6 p.m. They were fed *ad libitum* on an 18% casein diet containing 0.75% adenine, which produced experimental renal failure in the animals.⁹⁻¹²⁾ During the adenine feeding period, extracts of each prescription dissolved in water were administered orally for 24 days to rats as drinking water, while control rats received tap water. Throughout the experimental period, there were no statistically significant differences between the control and each of the extract-treated rats with regard to changes in body weight. The food intake of each rat was essentially proportional to weight change. No case of diarrheal symptom was found. Six rats were used for each experimental group. Values were expressed as means \pm S.E.

Prescriptions : The composition of Daiô-busi-tô used in the experiment was as follows : 10 g of Rhei Rhizoma, 30 g of Aconiti Tuber, and 20 g of Asiasari Radix. The extract was obtained as follows : the above-mentioned crude drugs were boiled gently in 1000 ml of water for 60 min and about 500 ml of decoction was obtained. The extract was then concentrated under reduced pressure to leave a brown residue at a yield of about 20%. The following prescriptions were obtained from Tsumura Juntendo, Inc., Tokyo, Japan (figures indicate proportions of each ingredient, expressed in parts per whole) : Tôkakuzyôki-tô (Persicae Semen 5, Cinnamomi Cortex 4, Rhei Rhizoma 3, Glycyrrhizae Radix 1, Natrium Sulfuricum 2), San'ô-syasin-tô (Rhei Rhizoma 3, Coptidis Rhizoma 3, Scutellariae Radix 3), Simotu-tô (Rehmanniae Radix 3, Paeoniae Radix 3, Cnidii Rhizoma 3, Angelicae Radix 3), Syô-

saiko-tô (Bupleuri Radix 7, Pinelliae Tuber 5, Scutellariae Radix 3, Zizyphi Fructus 3, Ginseng Radix 3, Glycyrrhizae Radix 2, Zingiberis Rhizoma 1), and Sairei-tô (Bupleuri Radix 7, Pinelliae Tuber 5, Scutellariae Radix 3, Zizyphi Fructus 3, Ginseng Radix 3, Glycyrrhizae Radix 2, Zingiberis Rhizoma 1, Alismatis Rhizoma 5, Atractylodis Lanceae Rhizoma 3, Polyporus 3, Hoelen 3, Cinnamomi Cortex 2). Hatimi-ziô-gan (Rehmanniae Radix 6, Corni Fructus 3, Dioscoreae Rhizoma 3, Alismatis Rhizoma 3, Hoelen 3, Moutan Cortex 2, Cinnamomi Cortex 1, Aconiti Tuber 0.5) was a product of Ohminedo Pharmaceutical Industry, Co., Ltd., Nara, Japan.

Analysis : On the 24th day of the feeding period, rats were stunned by a sharp blow on the head. Blood was collected into a conical centrifuge tube and the serum was separated by centrifugation immediately for determination of urea nitrogen, creatinine, guanidino compounds and electrolytes. Urea nitrogen, inorganic phosphate and calcium were determined using commercial reagents (BUN KAINOS obtained from Kainos Laboratories, Inc., Tokyo, Japan ; Phosphor B-Test Wako from Wako Pure Chemical Industries, Ltd., Osaka, Japan ; Calcium C-Test Wako from Wako Pure Chemical Industries, Ltd.). For determination of creatinine, methylguanidine and guanidinosuccinic acid, the serum was deproteinized by addition of trichloroacetic acid (final concentration, 10%). The supernatant obtained by centrifugation at 3000 rpm for 10 min was injected into a Japan Spectroscopic liquid chromatograph using a step-gradient system. A fluorescence spectrometer (excitation 365 nm, emission 495 nm ; model FP-210, Japan Spectroscopic Co., Tokyo, Japan) was used for detection of the substances on the column.

Statistics : The significance of differences between the control and extract-treated groups was tested using Student's *t*-test.

Results

Rhubarb-containing prescriptions

The results of administration of Daiô-busi-tô are shown in Fig. 1. The urea nitrogen value was

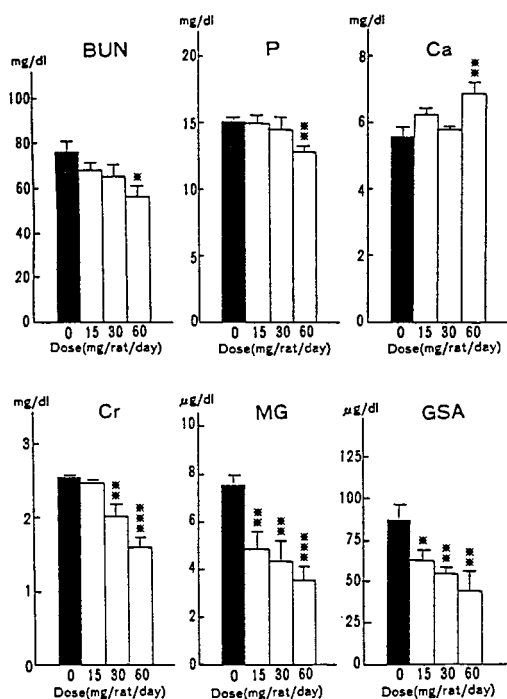


Fig. 1 Effect of Daiδ-busi-tō on serum constituents.

BUN, blood urea nitrogen ; Cr, creatinine ; MG, methylguanidine ; GSA, guanidinosuccinic acid ; P, inorganic phosphate ; Ca, calcium. Significantly different from the control value, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

significantly lowered in the group administered 60 mg of the extract and lowering tendencies were found in the group given doses of 15 and 30 mg. The creatinine value was also lowered significantly in the groups given 30- and 60-mg doses, while methylguanidine and guanidinosuccinic acid were remarkably decreased in all groups. Inorganic phosphate and calcium showed significant changes only in the group given a 60-mg dose. The results obtained with Tōkaku-zyōki-tō examined at doses of 12.5, 25 and 50 mg/rat/day showed that the urea nitrogen values were significantly lowered by as much as 35, 22 and 20%, respectively. The creatinine value was significantly lowered in the group given a 12.5-mg dose, and the groups given 25- and 50-mg doses also showed lowering tendencies. Both methylguanidine and guanidinosuccinic acid were significantly lowered in all groups. On the other hand, with regard to electrolytes, improvement of

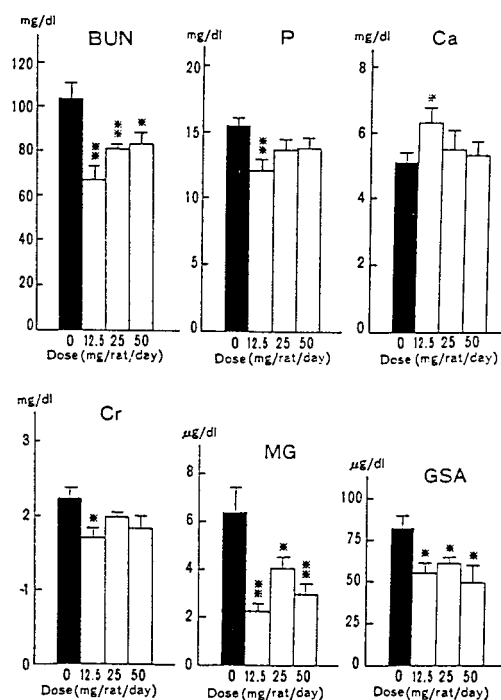


Fig. 2 Effect of Tōkaku-zyōki-tō on serum constituents.

Details are the same as in the legend to Fig. 1.

hyperphosphatemia and hypocalcemia was obtained in the group given a 12.5-mg dose but no change was seen in those given doses of 25 and 50 mg (Fig. 2). As shown in Fig. 3, the results of examination of the action of San'ō-syasin-tō at doses of 10, 25 and 40 mg/rat/day revealed that urea nitrogen, creatinine, inorganic phosphate and calcium did not vary in any group, and that guanidinosuccinic acid was significantly lowered only in the group given a 25-mg dose. The methylguanidine value in the groups given doses of 10, 25 and 40 mg was significantly decreased by as much as 50, 57 and 59%, respectively.

Prescriptions containing no rhubarb

When Hatimi-ziδ-gan was administered for 24 days, the urea nitrogen value was significantly lowered in the groups given 12.5- and 50-mg doses, as shown in Fig. 4. Creatinine and methylguanidine were significantly lowered only in the group given a 50-mg dose. Guanidinosuccinic acid showed a lowering tendency in the group

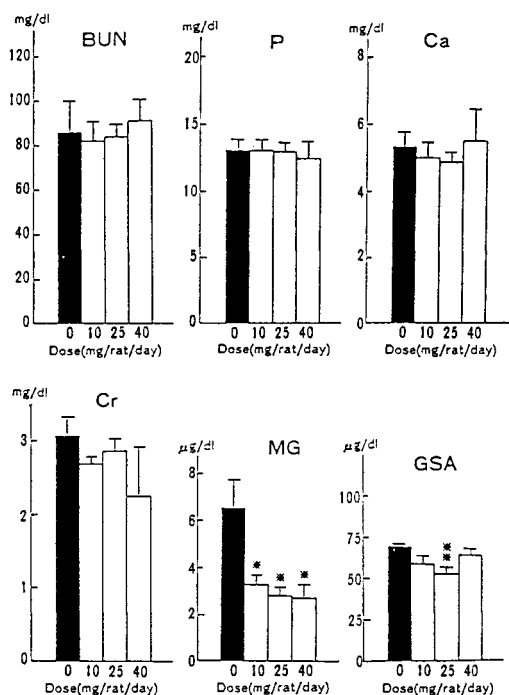


Fig. 3 Effect of San'δ-syasin-tō on serum constituents. Details are the same as in the legend to Fig. 1.

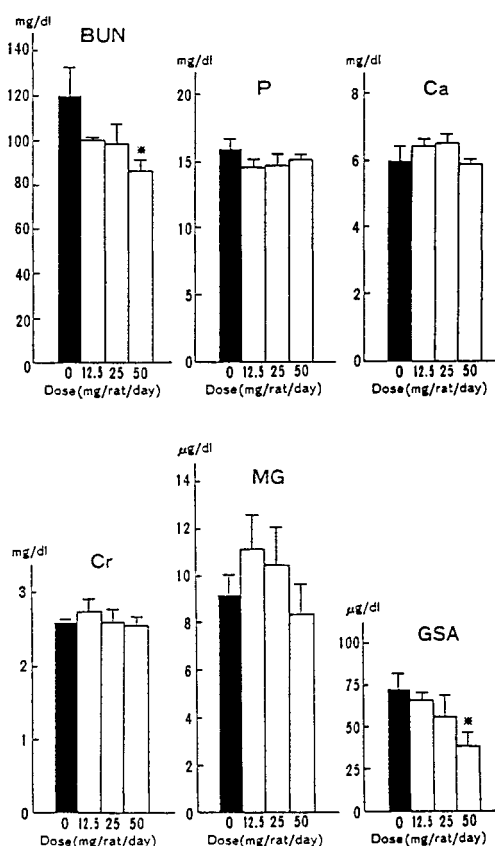


Fig. 5 Effect of Simotu-tō on serum constituents. Details are the same as in the legend to Fig. 1.

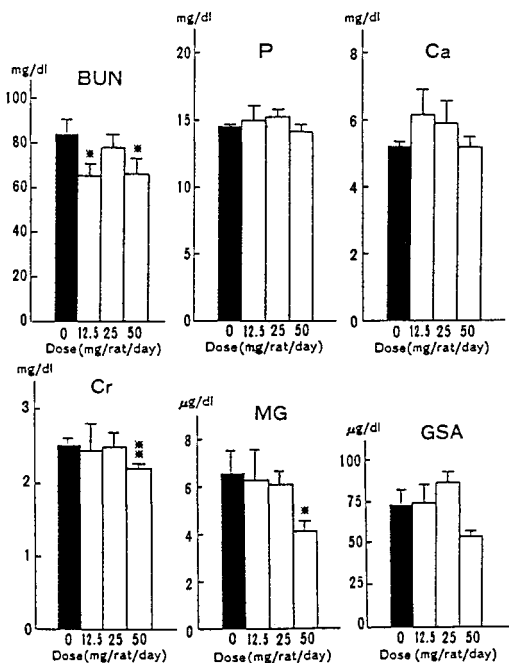


Fig. 4 Effect of Hatimi-zīδ-gan on serum constituents. Details are the same as in the legend to Fig. 1.

given a 50-mg dose, but inorganic phosphate and calcium values showed no change. Figure 5 shows the results of administration of Simotu-tō. The urea nitrogen value showed lowering tendencies in the groups given doses of 12.5 and 25 mg and was significantly lowered by 28% in the group given a 50-mg dose. Guanidosuccinic acid showed behavior similar to urea nitrogen, being significantly reduced in the 50-mg dose group. However, no change was observed in creatinine, methylguanidine, inorganic phosphate or calcium values. As shown in Fig. 6, when Syδ-saiko-tō was administered, no change was found in any of the values of urea nitrogen, creatinine, guanidosuccinic acid, inorganic phosphate or calcium, but methylguanidine showed a significant increase in the groups given doses of 10 and

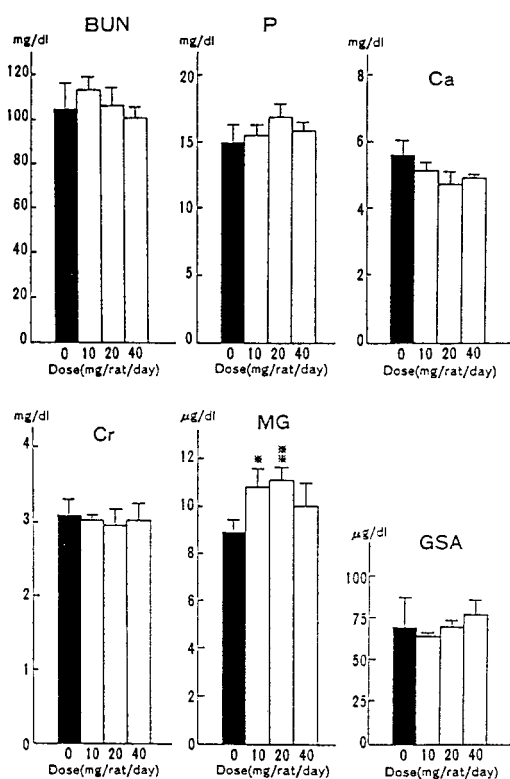


Fig. 6 Effect of Syō-saiko-tō on serum constituents.
Details are the same as in the legend to Fig. 1.

20 mg and an increasing tendency in the group given a 40-mg dose. The action of Sairei-tō was entirely different from those of the above 6 prescriptions, urea nitrogen, creatinine and methylguanidine being significantly increased, guanidinosuccinic acid and inorganic phosphate showing an increasing tendency, while calcium had a decreasing tendency accompanied by aggravated uremia.

Discussion

Daiō-busi-tō is described in *Jin-Gui-Yao-Lue* (金匱要略) and has been used by experience to treat slightly lowered physical strength, constipation with stomachache, coldness of the limbs and other symptoms, and to treat nephrolithiasis, cholelithiasis, spasm of the gastrointestinal tract and other symptoms in the modern medical science.¹³⁾ Tōkaku-zyōki-tō is described in *Shang-*

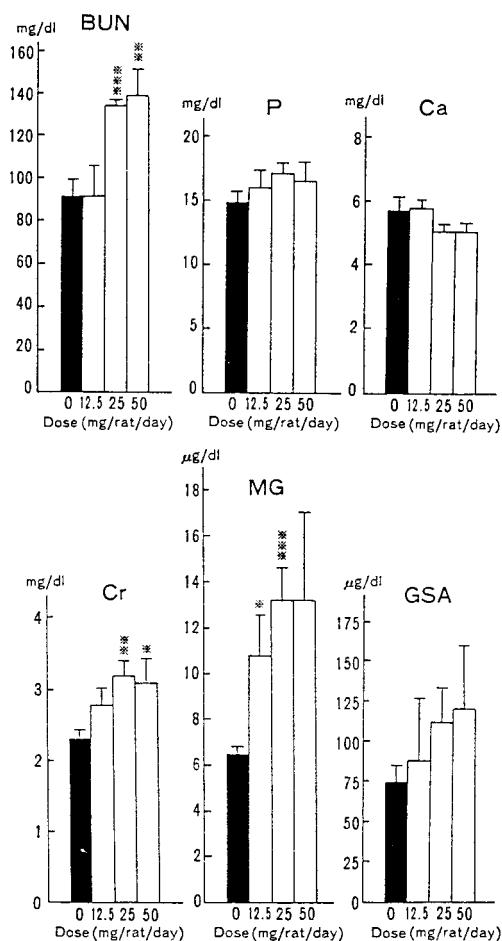


Fig. 7 Effect of Sairei-tō on serum constituents.
Details are the same as in the legend to Fig. 1.

Han-Lun (傷寒論), published in the Han era is, and is effective for treating constipation and menstrual disorders in persons who are relatively strong physically.¹⁴⁾ San'ō-syasin-tō is also described in *Jin-Gui-Yao-Lue* (金匱要略) together with Daiō-busi-tō and is applied for persons who have a good constitution and physical strength with a flushed face due to a rush of blood to the head and complaints of constipation tendency, epistaxis, hematemesis and other symptoms,¹⁵⁾ namely for the treatment of "Shi-Zheng" (実証) and "Re-Zheng" (熱証). Therefore, the component crude drugs are Rhei Rhizoma, Coptidis Rhizoma and Scutellariae Radix. All the prescriptions mentioned above contain Rhei Rhizoma ;

37.5% in Daiô-busi-tô, 20.0% in Tôkaku-zyôki-tô, and 33.3% in San'ô-syasin-tô.

These three prescriptions containing rhubarb lowered methylguanidine levels remarkably like the effect of both rhubarb alone¹⁶⁻¹⁸⁾ and Onpi-tô,^{1,2,5)} which contains about 43% rhubarb. On the other hand, Daiô-busi-tô and Tôkaku-zyôki-tô were found to have an action of significantly lowering urea nitrogen, creatinine, guanidinosuccinic acid and inorganic phosphate, and an effect of improving hypocalcemia which was not found in Onpi-tô. Though further examinations will be required in order to clarify the causes of these differences, as the composite crude drugs other than rhubarb, Daiô-busi-tô contains Aconiti Tuber and Asiasari Radix, while Tôkaku-zyôki-tô contains Persicae Semen, Cinnamomi Cortex, Glycyrrhizae Radix and Natrium Sulfuricum. Daiô-busi-tô, containing such "warm" drugs (Han-Zheng (寒証)-cured drugs in Chinese medicine¹⁹⁾) as Aconiti Tuber and Asiasari Radix, has a similar composition to Onpi-tô (a "warm" drug and "cold" drug, namely a Re-Zheng (熱証)-cured drug¹⁹⁾) but the former has a slightly smaller content of rhubarb. From this fact, it might be suggested that the lower content of rhubarb would weaken the improving action on nitrogen metabolism. On the other hand, with Tôkaku-zyôki-tô, which contains such "cold" drugs as Persicae Semen, used for treating blood stagnation and laxation, and Natrium Sulfuricum, the improving action on uremia was conversely decreased with increasing dose. This finding suggests that the effect of Natrium Sulfuricum, namely a "cold" effect, was so prominent that it produced an undesirable outcome. San'ô-syasin-tô, containing only "cold" drugs, showed no action in improving uremia other than a lowering of methylguanidine, and the results obtained apparently supported the above suggestion. An action of lowering methylguanidine has been observed only in prescriptions containing rhubarb, with rhubarb alone¹⁶⁻¹⁸⁾ and also with Onpi-tô.^{1,2,5)} These results therefore may suggest that the above action is specific to rhubarb.

On the other hand, Hatimi-ziô-gan, a prescription containing no rhubarb, is also described

in *Jin-Gui-Yao-Lue* (金匱要略). Its indication is stated to be "Shen-Yang-Xu" (腎陽虛) and it has been used to treat debility of the abdomen and lower limbs, coldness and numbness, and in modern medicine it is applied to urination disturbance, thirst and edema in nephritis and nephrosis.²⁰⁾ Simotu-tô, described in *He-Ji-Ju-Fang* (和劑局方), improves blood supply as well as refreshing the blood,²¹⁾ while Syô-saiko-tô, described in *Shang-Han-Lun* (傷寒論), is extensively used to treat hepatitis, nephritis, chronic gastrointestinal disorders and other conditions.²²⁻²⁴⁾ Sairei-tô has been applied for cases of decreased urination, edema, proteinuria and other disorders, and Abe *et al.*,²⁵⁾ Okada *et al.*,²⁶⁾ and Miyakawa *et al.*²⁷⁾ have reported its therapeutic effects on experimental and clinical nephrotic syndrome. Among the 4 prescriptions containing no rhubarb, the blood concentrations of such uremia-causing substances as urea nitrogen, creatinine and methylguanidine were found to be lowered in the group given Hatimi-ziô-gan at the largest dose of 50 mg, while lowering of the concentration of urea nitrogen and guanidinosuccinic acid was observed in the group given the largest dose of Simotu-tô. However, no such actions were found with Syô-saiko-tô at all, and in fact uremia was aggravated by using Sairei-tô, indicating that the uremia-improving action observed with the rhubarb-containing prescriptions was not observed with the latter preparations.

From the above findings, it is considered that rhubarb is the common essential component in prescriptions with a uremia-improving action, and that a "warm" drug which softens the "Han" (寒) property of rhubarb itself is present. From this view point, it is suggested that Onpi-tô, as reported previously,¹⁻⁶⁾ and Daiô-busi-tô as shown in the present experimental results, are useful for the conservative treatment of kidney disease. Since prescriptions such as Syô-saiko-tô and Sairei-tô, which have been used to treat nephritis and nephrosis, have a rather weak action, it is supposed that they do not act directly on the immunological system on the renal glomeruli, but enhance metabolism in the body, and that this effect is involved in the action mechanism of

rhubarb. From the findings that this effect was observed in the groups which received Onpi-tô and Daiô-busi-tô, and also in the group given the largest dose of Hatimi-zîô-gan, it is considered that the rats used in this experiment had "Pi-Yang-Xu" (脾陽虚), partly coexisting with "Shen-Yang-Xu" (腎陽虚) through analysis of "Zheng" (証) used in classical Chinese medicine. Further future studies will be required in order to obtain more detailed information.

和文抄録

大黃含有方剤並びに腎疾患に用いられている方剤7種を選び、腎不全ラットに対する作用を検討した。その結果、大黃附子湯では血清尿素窒素(60 mg投与群)、クレアチニン(30, 60 mg)、メチルグアニジン、グアニジノコハク酸(15, 30, 60 mg)、無機リン(60 mg)がいずれも有意に低下し、カルシウム値の改善は60 mgで認められた。桃核承気湯は投与量の最も低い12.5 mgで尿素窒素、クレアチニン、メチルグアニジン、グアニジノコハク酸、無機リンの有意な低下、カルシウムの有意な増加を認めた。三黄瀉心湯はメチルグアニジンの低下以外はいずれも有意な変化を認めなかった。八味地黄丸(尿素窒素、クレアチニン、メチルグアニジン)、四物湯(尿素窒素、グアニジノコハク酸)はいずれも投与量の最も多い50 mgで有意な低下作用を認めた。他方、小柴胡湯は逆にメチルグアニジンが増加し、尿毒症の改善は認められなかった。柴苓湯も尿素窒素、クレアチニン、メチルグアニジンが有意に増加し、尿毒症状の悪化傾向を認めた。

References

- Oura, H., Zheng, P.D. and Yokozawa, T.: Effect of Onpi-tô in rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* 1, 209-217, 1984
- Oura, H., Chung, H.Y., Zheng, P.D., Yokozawa, T., Wakaki, K. and Koizumi, F.: Effect of Onpi-tô administered orally for a long term on rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* 2, 365-371, 1985
- Zheng, P.D., Yokozawa, T., Oura, H., and Nakada, T.: Effect of orally administered Onpi-tô to rats with chronic renal failure on blood flow in renal tissue, blood pressure, and hormone levels in blood. *J. Med. Pharm. Soc. WAKAN-YAKU* 3, 37-44, 1986
- Zheng, P.D., Yokozawa, T. and Oura, H.: Effect of Onpi-tô on extrarenal hormones in rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* 3, 65-70, 1986
- Zheng, P.D., Yokozawa, T. and Oura, H.: Effect of Onpi-tô in adenine-induced chronic renal failure rats. *J. Med. Pharm. Soc. WAKAN-YAKU* 3, 83-88, 1986
- Yokozawa, T., Zheng, P.D., Mo, Z.L. and Oura, H.: The effect of Onpi-tô on urinary excretion of methylguanidine in rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* 3, 198-201, 1986
- Mitsuma, T., Terasawa, K., Yokozawa, T. and Oura, H.: Rhubarb therapy in patients with chronic renal failure (Part 1). *J. Med. Pharm. Soc. WAKAN-YAKU* 1, 266-278, 1984
- Mitsuma, T., Yokozawa, T., Oura, H. and Terasawa, K.: Rhubarb therapy in patients with chronic renal failure (Part 2). *Jap. J. Nephrol.* 29, 195-207, 1987
- Yokozawa, T., Zheng, P.D., Oura, H. and Koizumi, F.: Animal model of adenine-induced chronic renal failure in rats. *Nephron.* 44, 230-234, 1986
- Yokozawa, T. and Oura, H.: Distribution of guanidino compounds in rats with chronic renal failure induced by adenine. *Jap. J. Nephrol.* 29, 1137-1143, 1987
- Yokozawa, T., Oura, H. and Nakada, T.: Blood flow in renal tissue, blood pressure, and blood hormone levels in rats with adenine-induced renal failure. *Jap. J. Nephrol.* 29, 1145-1151, 1987
- Yokozawa, T., Chung, H.Y. and Oura, H.: Urinary constituents and renal function in rats administered with adenine. *Jap. J. Nephrol.* 29, 1129-1135, 1987
- Wen Xia. In "Zhong Yi Fang Ji Lin Chuang Shou Ce" (Ed. by Shanghai College of Traditional Chinese Medicine), Shanghai Technology's Publisher, Shanghai, pp. 53-54, 1982
- Han Xia. In "Zhong Yi Fang Ji Lin Chuang Shou Ce" (Ed. by Shanghai College of Traditional Chinese Medicine), Shanghai Technology's Publisher, Shanghai, pp. 49-53, 1982
- Coptidis Rhizoma. In "Kanyaku no Rinsho Ohyo" (Ed. by Chuzan Igakuin), Ishiyaku Shuppan, Tokyo, pp. 98-100, 1980
- Yokozawa, T., Suzuki, N., Zheng, P.D., Oura, H. and Nishioka, I.: Effect of orally administered rhubarb extract in rats with chronic renal failure. *Chem. Pharm. Bull.* 32, 4506-4513, 1984
- Yokozawa, T., Suzuki, N., Okuda, I., Oura, H. and Nishioka, I.: Uremia-preventive effect of rhubarb extract in rats. *J. Med. Pharm. Soc. WAKAN-YAKU* 2, 344-350, 1985
- Yokozawa, T., Suzuki, N., Oura, H., Nonaka, G. and Nishioka, I.: Effect of extracts obtained from rhubarb in rats with chronic renal failure. *Chem. Pharm. Bull.* 34, 4718-4723, 1986
- Zhong Cao Yao de Xing Neng. In "Zhong Cao Yao Xue" (Ed. by Shanghai College of Traditional Chinese Medicine), Shanghai People's Publisher, Shanghai, pp.

- 9-12, 1974
- 20) Bu Yang. In "Zhong Yi Fang Ji Lin Chuang Shou Ce" (Ed. by Shanghai College of Traditional Chinese Medicine), Shanghai Technology's Publisher, Shanghai, pp. 212, 1982
- 21) Bu Xue. In "Zhong Yi Fang Ji Lin Chuang Shou Ce" (Ed. by Shanghai College of Traditional Chinese Medicine), Shanghai Technology's Publisher, Shanghai, pp. 195-196, 1982
- 22) He Jie Shao Yang. In "Zhong Yi Fang Ji Lin Chuang Shou Ce" (Ed. by Shanghai College of Traditional Chinese Medicine), Shanghai Technology's Publisher, Shanghai, pp. 59-60, 1982
- 23) Makisaka, Y., Oka, T., Matsubara, T., Hamada, Y., Aoyama, S., Odahara, M., Sakata, K., Nishioka, M. and Takemoto, T. : Long-term treatment of chronic hepatitis with Shosaikoto and Keishibukureogan. *Proc. Symp. WAKAN-YAKU* **14**, 37-44, 1981
- 24) Yamamoto, M., Uemura, T., Nakama, S., Uemiya, M., Hara, H., Koyama, T., Hayashi, Y., Tosa, H., Imadaya, A., Masuda, Y. and Kumagai, A. : Effects of saikosaponins and prescriptions including bupleurum falcatum on chronic hepatitis (The 2nd report). *Proc. Symp. WAKAN-YAKU* **14**, 56-59, 1981
- 25) Abe, H., Orita, M., Konishi, H. and Arichi, S. : Effects of Sairei-tô on aminonucleoside nephrosis in the rats. *J. Med. Pharm. Soc. WAKAN-YAKU* **3**, 24-30, 1986
- 26) Okada, T., Yamatani, M., Wada, H. and Uchino, H. : Crude drug treatment of the nephrotic syndrome in childhood. *J. Med. Pharm. Soc. WAKAN-YAKU* **2**, 468-471, 1985
- 27) Miyakawa, S., Usui, N. and Akatsuka, J. : Renal disease. *Pediatr. Med.* **17**, 603-608, 1985