Original

Effects of Syô-saiko-tô and Dai-saiko-tô on experimental atherosclerosis in rabbits

Masaomi Umeda, Sakae Amagaya and Yukio Ogihara*

Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Nagoya City University

Abstract

Effects of the oral treatment of Syô-saiko-tô and Dai-saiko-tô on the experimental atherosclerosis in rabbits fed 0.75% cholesterol diet for 6 months were investigated. A recently publicized non-invasive optical measurement of volume elastic modulus (Ev) was applied for indirect evaluation of atherosclerosis. After the removal of thoracic aorta of all rabbits at the 6th month, atherosclerotic lesions were studied histopathologically. Hydroxyproline obtained by the hydrolysis of aortic collagen and lipid content in both serum and thoracic aorta were also determined. It was found that Syô-saiko-tô and Dai-saiko-tô improved the cholesterol-induced atherosclerosis. Namely, both Kampô-hôzai had effect on Ev histopathological findings, atherosclerotic index, aortic lipid and aortic hydroxyproline content. Judging from these indices, Syô-saiko-tô was more effective than Dai-saiko-tô. Both Kampô-hôzai, however, had no effect on serum cholesterol. These results suggest that Syô-saiko-tô and Dai-saiko-tô improve the hyperlipidemia-induced injury of aortic endothelial and/or smooth muscle cells.

Key words atherosclerosis, optical non-invasive measurement, aortic lipid, aortic hydroxyproline, Syô-saiko-tô, Dai-saiko-tô.
Abbreviations Kampô-hôzai, 漢方方剤; Dai-saiko-tô (Da-Chai-Hu-Tang), 大柴胡湯; Syô-saiko-tô (Xiao-Chai-Hu-Tang), 小柴胡湯.

Introduction

Some Kampô - hôzai (Japanese and Chinese traditional medicines) have been clinically used for the treatment of hyperlipidemia, hypertension, diabetes mellitus and fatness which are considered to be the factors of atherosclerosis, and they are expected to be beneficial for the therapy of atherosclerosis. Teramoto et al.[1] reported that Dai-saiko-tô, an extract from the mixture of 8 herbal drugs, reduced serum total cholesterol in an animal model fed a high cholesterol diet. Furthermore, Ohminami et al.[2] reported that Dai-saiko-tô reduced serum triglyceride level in hyperlipidemia rats. These reports show that Dai-saiko-tô can restore the hyperlipidemia and the subse-

quent atherosclerosis. While, Yamamoto et al.[3] reported that Syô-saiko-tô, an extract from the mixture of 7 herbal drugs and five of them which are common to the herbal drugs of Dai-saiko-tô, reduced serum cholesterol in hypercholesterolemia rat. This suggests that Syô-saiko-tô is also beneficial for the therapy of hypercholesterolemia and atherosclerosis.

In the objective assessment of various vascular regions such as atherosclerosis, a non-invasive measurement of dynamic arterial wall characteristics is extremely improtant. A non-invasive measurement is also useful in more basic studies such as the assessment of elastic behavior during various physiological conditions used in the experimental mode. Kamiya et al.[4,5] developed the non-invasive measurement using a photoelec-

*〒 467 名古屋市瑞穂区田辺通 3-1
名古屋市立大学薬学部生薬学教室　荻原幸夫
3-1, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

tric measurement system, and they applied it to the study of the elastic characteristics of the arterial vascular bed including medium and small sized arteries within the forearm of rabbits. In our previous paper,[6] we reported that volume elastic modulus (Ev) obtained by non-invasive optical measurement was responsible for the sclerosis of blood vessels, area of atherosclerosis within the vascular lumen, lipid accumulation in the blood vessel wall and vascular wall collagen content.

In this paper, the effects of Dai-saiko-tô and Syô-saiko-tô on the experimental atherosclerosis in rabbits fed a cholesterol-rich diet for 6 months were examined by non-invasive optical measurement in addition to the conventional histological findings, the measurement of serum or aortic lipid contents and the determination of hydroxyproline in aortic collagen.

Materials and Methods

Animals : Male New Zealand white rabbits weighing about 2 kg were purchased from Nippon Bio. Supp. Center (Tokyo, Japan). They were kept in an air conditioned room and given water *ad libitum*.

Drugs : Dai-saiko-tô, Syô-saiko-tô and soysterol as a standard drug were obtained from Tsumura Juntendo Inc. (Tokyo, Japan). The combination of herbal drugs in Dai-saiko-tô and Syô-saiko-tô is shown in Table I.

Experimental design : Rabbits were divided into 6 groups of 8 rabbits each. The normal group was maintained daily with a commercial diet (CR-3 : Nihon Crea, Aichi, Japan) at a dose of 40 g/kg body weight. The control group was fed a 0.75% cholesterol-contained CR-3. Other groups were fed a 0.75% cholesterol diet containing powdered extracts of Kampô-hôzai or soysterol. All groups were bred for 6 months to induce atherosclerosis.

Assay of serum cholesterol and phospholipids : Blood was collected every 2 weeks from the marginal ear vein following an overnight fast for 16 hr and serum was prepared by centrifugation. Serum cholesterol and phospholipid were determined using enzymatic reagent kits (Iatro-lipo TC and Iatroset PL-E, Iatron, Tokyo, Japan).

Table I Crude drug composition of the Kampô-hôzai.

Herbal drug (Plant name)	Family (part used)	Composition (g)	
		Syô-saiko-tô	Dai-saiko-tô
Glycyrrhizae Radix (*Glycyrrhiza glabra* L.)	Legminosae (Root)	2.0	—
Ginseng Radix (*Panax ginseng* C.A. MEYER)	Araliaceae (Root)	3.0	—
Bupleuri Radix (*Bupleurum falcatum* L.)	Umbelliferae (Root)	7.0	6.0
Scutellariae Radix (*Scutellaria baicalensis* GEORGI)	Labiatae (Root)	3.0	—
Zingiberis Rhizoma (*Zingiber officinale* ROSCOE)	Zingiberaceae (Rhizoma)	4.0	4.0
Paeoniae Radix (*Paeonia lactiflora* PALLAS)	Paeoniaceae (Root)	—	3.0
Pinelliae Tuber (*Pinellia ternata* BREITENBACH)	Araceae (Tuber)	5.0	4.0
Zizyphi Fructus (*Zizyphus vulgsris* LAM.)	Rhamnaceae (Fruit)	3.0	3.0
Rhei Rhizoma (*Rheum tanguticum* MAXIM.)	Polygonaceae (Rhizoma)	—	2.0
Aurantii Fructus IMMATURUS (*Citrus aurantium* L.)	Rutaceae (Fruit)	—	2.0

Measurement of volume elastic modulus (Ev) : Non-invasive measurement of atherosclerotic changes in the arterial system was done according to the method reported by Kamiya and Shimazu.[4,5] They developed a nontraumatic technique to measure the *in vivo* pressure-volume relationship between the infrared light absorption through the tissue and blood volume contained in it as the principle. The system designed for this purpose consisted of a light source, a photodetector, a compressing cuff drived by a micro-roller pump and the amplifier for the phototransistor output and for the cuff compression pressure. The light source and detector tips were directly fixed on the rabbit forearm skin in mutually opposing positions, and the compression cuff was placed around the forearm so as to cover the tips at the middle portion. As the compression pressure of the cuff was gradually increased, the transmural pressure of the vessels under the cuff was reduced, and the associated decrease in blood volume according to the overall vascular compliance was detected by the change in the transmitted light intensity proportional to the transistor output. The relative pressure-volume relationship normalized with the unstressed vascular volume was obtained for the arterial system, as well as Ev for various level of the transmural pressure.

Extripation of aorta : At the end of 6 months of feeding, rabbits were sacrificed under anaesthesia with sodium pentobarbital at a dose of 26 mg/kg after the collection of blood from a mesentric vein. Fatty and connective tissues were carefully removed from the thoracic aorta (8.5 cm) which was weighed and performed by taking pictures. Atherosclerotic index was expressed as the ratio of the area of atherosclerotic regions against that of thoracic intimal surface.

Determination of aortic lipids : The adventitia was carefully removed from an aorta, a part of which was cut into a small segment and homogenized with 1.0 ml of water. After the addition of 6.0 ml of chloroform/methanol (1 : 2 v/v) to the homogenate, the mixture was homogenized again and centrifuged. The resultant residue was homogenized again with chloroform/methanol/water (1 : 2 : 0.8 v/v) and centrifuged. The resultant organic layer was combined and mixed well after the addition of 3.0 ml of water and chloroform. The lower layer was collected and evaporated with a stream of nitrogen. The resultant lipid fraction was determined using an enzymatic reagent kit.

Determination of aortic hydroxyproline content : The residue of the aorta after the extraction of lipids was dried *in vacuo*. Residue, 10 mg, and conc. HCl, 1.5 ml, were placed in a screw-capped tube, and the tube was heated in an oil bath at 110℃ overnight. After hydrolysis, pH of sample was adjusted to 7.0 with 6 N KOH. An appropriate aliquot of the hydrolyzed solution containing 3 to 12 μg of hydroxyproline was placed in another screw-capped tube, and the final volume of each sample was adjusted to 4 ml by adding distilled water. Determination of hydroxyproline was performed using the Ehrlich's reagent according to the method by Prockop *et al.*[7]

Histological studies : A portion of the aorta from each animal at the 6th month was fixed in 10% formalin, embedded in paraffin and stained with hematoxylin and eosin or azan.

Presentation of data : Significant differences were calculated by *t*-test.

Results

Body weight and serum lipid levels

Body weight increased in a time dependent manner, while there was no significant difference between the different diet groups as shown in Fig. 1. Serum cholesterol and phospholipid were increased by feeding a cholesterol-rich diet as shown in Fig. 2. Serum cholesterol reached the maximum level at 8 weeks and was constantly maintained after 12 weeks. The variation of serum phospholipid was similar to that of cholesterol. Soysterol at a dose of 1.2 g/kg which was correspondent to 60 times the human dose per day inhibited the increased serum cholesterol and phospholipid level drastically. But, soysterol at a dose of 0.2 g/kg which was correspondent to 10 times the human dose per day never decreased them. Dai-saiko-tô at a dose of 0.9 g/kg which

was equal to 10 times the human dose per day also showed no inhibition on cholesterol-induced hypercholesterolemia, while Syô-saiko-tô at a dose of 0.9 g/kg which was also equal to 10 times the human dose per day showed the tendency to in-

hibit the increase of phospholipid level after 16 weeks.

Optical non-invasive measurement of atherosclerosis
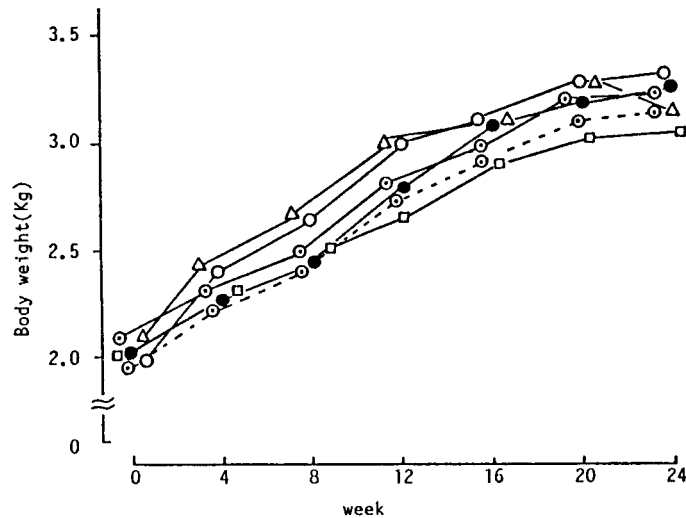
Ev in each group was not variated up to 12

Fig. 1   Increase of body weights in rabbits fed on various diets.
   Diet compositions are as described in "Materials and Methods." —□— : normal, —●— : cholesterol, —○— : cholesterol+Syô-saiko-tô 0.9 g/kg, —△— : cholesterol+Dai-saiko-tô 0.9 g/kg, —⊙— : cholesterol+soysterol 1.2 g/kg, ⋯⊙⋯ : cholesterol+soysterol 0.2 g/kg. Each point indicates the mean of 8 rabbits.
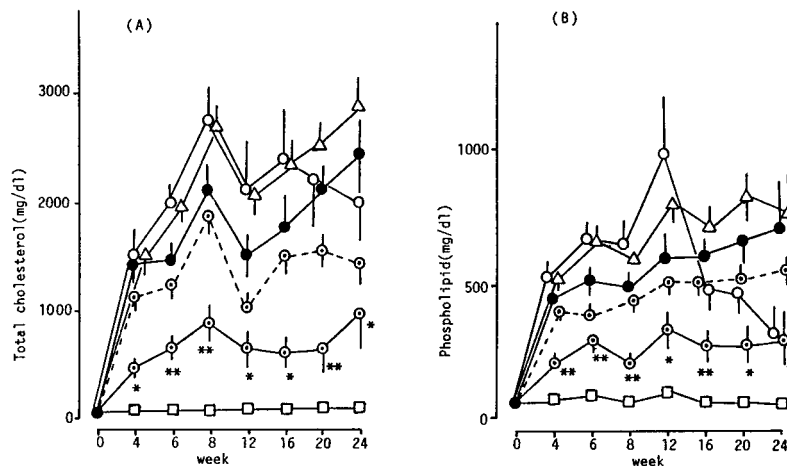

Fig. 2   Change of serum cholesterol and phospholipid levels of rabbits fed on various diets. (A) : serum cholesterol, (B) : serum phospholipid. Diet compositions are as described in "Materials ans Methods." —□— : normal, —●— : cholesterol, —○— : cholesterol+Syô-saiko-tô 0.9 g/kg, —△— : cholesterol+Dai-saiko-tô 0.9 g/kg, —⊙— : cholesterol+soysterol 1.2 g/kg, ⋯⊙⋯ : cholesterol+soysterol 0.2 g/kg. Vertical bars indicate S.E.M. of 8 rabbits. $*p<0.05$ and $**p<0.01$ vs. cholesterol group.
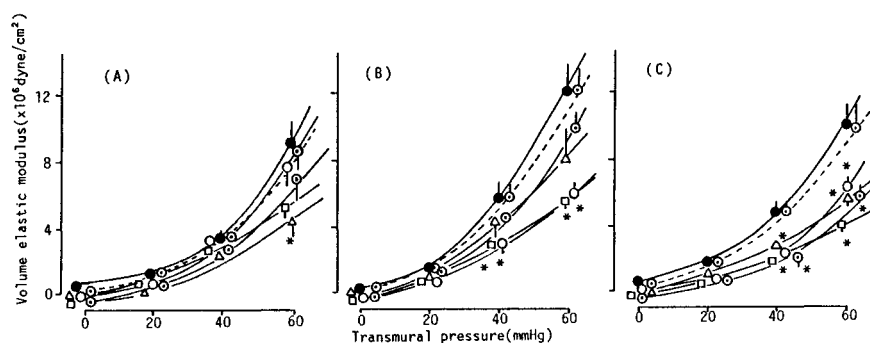
Fig. 3　Change of volume elastic modulus (Ev) in rabbits fed on various diets.
　　(A) : 16 weeks, (B) : 20 weeks, (C) : 24 weeks. Diet compositions are as described in
　　"Materials and Methods." —　—: normal, —●—: cholesterol, —○—: cholesterol + Syô-
　　saiko-tô 0.9 g/kg, —△—: cholesterol + Dai-saiko-tô 0.9 g/kg, —⊙—: cholesterol + soyste-
　　rol 1.2 g/kg, ⋯⊙⋯: cholesterol + soysterol 0.2 g/kg. Vertical bars indicate S.E.M. of 8 rab-
　　bits. *$p < 0.05$ vs. cholesterol group.

weeks. As shown in Fig. 3, Ev value, however, increased drastically in the cholesterol treated control group after 20 weeks at 40 and 60 mmHg of transmural pressure. The cholesterol-induced increase of Ev value at 20 weeks was inhibited by Syô-saiko-tô only. Dai-saiko-tô and both doses of soysterol showed no significant inhibition. On the other hand, cholesterol-induced increase of Ev value at 24 weeks was inhibited by Syô-saiko-tô and Dai-saiko-tô in a significant manner. Soysterol at a dose of 1.2 g/kg also inhibited it, but soysterol at a dose of 0.2 g/kg never affected the increased Ev value up to 24 weeks.

Atherosclerotic index in aorta

Effect of Kampô-hôzai on atherosclerotic index was shown in Fig. 4. Syô-saiko-tô and Dai-saiko-tô were found to decrease the area of atherosclerotic lesion. Soysterol at a dose of 1.2 g/kg decreased it remarkably, while soysterol at a dose of 0.2 g/kg showed no inhibition.

Histopathological studies of aorta

Table II summarizes the histopathological findings of thoracic aorta. It was found that the cholesterol treated control group had a very thick intima, a little accumulation of foam cell, serious hyperplasia of collagen, serious calcium deposit and numerous necrotic substances. Syô-saiko-tô treated animals restored the histopathological findings of intima as well as soysterol at a
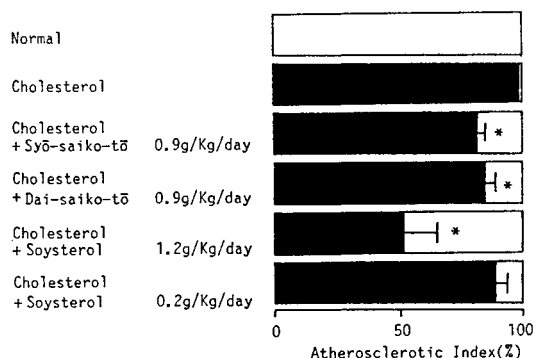

Fig. 4　Atherosclerotic index in thoracic aorta of rabbits fed on various diets.
　　Diet compositions are as described in "Materials and Methods." ■: Area of atherosclerosis on surface of thoracic aorta. Each column indicates the mean±S.E. of 8 rabbits. *$p < 0.05$ vs. cholesterol group.

dose of 1.2 g/kg treated group. Especially, the decrease of hyperplasia of collagen, calcium deposit and necrotic substances by the treatment of Syô-saiko-tô was attractive. In media, tear of elastic lamina was also restored by Syô-saiko-tô. Dai-saiko-tô also showed a restoration on histopathological findings, although its effect was weaker than that of Syô-saiko-tô. Soysterol at a dose of 0.2 g/kg showed no effect on histopathological finding.

Table II   Histopathological findings of intima and media of rabbits fed on various diets.

Group	Dose (g/kg/day)	Thickening Max (μm)	Thickening Range	Accumlation of Foam Cell	Crystal of Cholesterin	Hyperplasia of Collagen	Calcium Deposit	Substance of Necrosis
				Histopathological Findings of Intima				
Normal		0	—	—	—	—	—	—
Cholesterol		563	+++	+	+	++	++	++
Cholesterol +Syô-saiko-tô	0.9	477	+++	++	+	+	+	+
Cholesterol +Dai-saiko-tô	0.9	573	++++	++	++	++	+	++
Cholesterol +Soysterol	1.2	283	++	+	+	+	—	—
Cholesterol +Soysterol	0.2	605	++++	+	+	++	++	++

Group	Dose (g/kg/day)	Lipid Deposit	Hyperplasia of Collagen	Tear of Elastic Lamina	Calcium Deposit
		Histopathological Findings of Media			
Normal		—	—	—	—
Cholesterol		+	+	++	+
Cholesterol +Syô-saiko-tô	0.9	+	+	+	—
Cholesterol +Dai-saiko-tô	0.9	+	+	++	—
Cholesterol +Soysterol	1.2	+	+	+	—
Cholesterol +Soysterol	0.2	+	+	+	+

Each value indicates the mean of 8 rabbits. — : normal, + : very light, ++ : light, +++ : moderate, ++++ : strong.

Aorta weight and lipid content

Aorta weight and aorta lipid content are indicated in Table III. Cholesterol feeding increased the aorta weight about 3-fold over that of the normal group. Aorta lipid content was also increased drastically on control group. Both Kampô-hôzai showed no significant effect on the increased aorta weight. They, however, inhibited the cholesterol-induced increase of aortic total cholesterol and phospholipid as well as the treatment of 1.2 g/kg of soysterol, although soysterol at a dose of 0.2 g/kg showed no inhibition on both aorta weight and lipid content.

Aorta hydroxyproline content

Hydroxyproline which was a hydrolyzed product from aortic collagen was determined as a hardening index of thoracic aorta, and the results are summarized in Fig. 5. By the cholesterol feeding, hydroxyproline was increased approximately 2-fold over that of the normal group. Syô-saiko-tô and soysterol at a dose of 1.2 g/kg had a similar inhibitory effect on cholesterol-induced increase of aortic hydroxyproline content (mg/aorta and μg/mg protein). Dai-saiko-tô also inhibited the increase of hydroxyproline (μg/mg protein), while soysterol at a dose of 0.2 g/kg was not effective.

Table III Aorta weight and aorta lipid content in rabbits fed on various diets.

Group	Dose (g/kg/day)	Aorta weight		Aorta lipid content (mg/aorta)	
		(mg)	(mg/kg b.w.)	TC	PL
Normal		446±53**	146±17**	0.66±0.06**	2.21±0.30**
Cholesterol		1365±132	433±51	57.14±8.12	40.99±6.62
Cholesterol +Syô-saiko-tô	0.9	1112±60	352±26	33.57±4.88*	16.77±2.06*
Cholesterol +Dai-saiko-tô	0.9	1106±176	348±56	29.81±4.00	16.88±2.66*
Cholesterol +Soysterol	1.2	585±93**	190±35**	12.63±5.02**	6.49±2.87**
Cholesterol +Soysterol	0.2	1379±97	454±37	50.30±3.70	24.70±3.03*

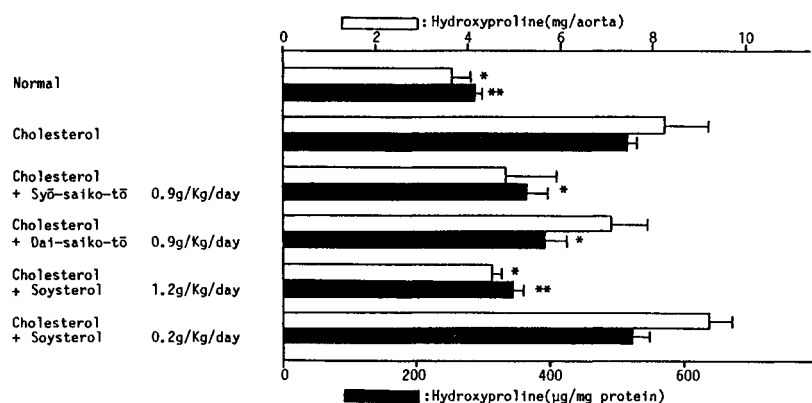Each value indicates the mean±S.E. of 8 rabbits. *$p<0.05$ and **$p<0.01$ vs. cholesterol group.

Fig. 5 Change of hydroxyproline content in aorta of rabbits fed on various diets.
Diet compositions are as described in "Materials and Methods." ▮ : hydroxyproline
(μg/mg protein), ☐ : hydroxyproline (mg/aorta). *$p<0.05$ and **$p<0.01$ vs. cholesterol group.

Discussion

It was observed that oral administration of Syô-saiko-tô and Dai-saiko-tô at doses of 0.9 g/kg which were almost equal to 10 times the human dose per day had an improving effect on volume elastic modulus which represents the extent of atherosclerosis. Furthermore, both Kampô-hôzai were effective on the histopathological findings, aortic lipid content and aortic hydroxyproline content which was the indication of collagen hyperplasia. Serum cholesterol levels were not improved in Syô-saiko-tô and Dai-saiko-tô treated group, although Syô-saiko-tô decreased

the serum phospholipid level after 16 weeks. On the other hand, soysterol at a dose of 1.2 g/kg which was almost equal to 60 times the human dose per day inhibited all the indices, while soysterol at a dose of 0.2 g/kg showed no effect. The anti-atherosclerotic action of soysterol was reported to inhibit the exogenous cholesterol absorption from intestine.[10,11] Ineffectiveness of Syô-saiko-tô and Dai-saiko-tô on hypercholesterolemia could be assumed that both Kampô-hôzai protect the hypercholesterolemia-induced injury of aorta endothelial cells and/or smooth muscle cells. Our previous paper described the inhibitory action of Syô-saiko-tô and Dai-saiko-tô on collagen-induced platelet aggregation.[8] Both

Kampô-hôzai are expected to inhibit thromboxane A_2 synthesis, since baicalin and baicalein involved in *Scutellaria baicalensis* root are reported to inhibit lipoxygenase activity.[9] These data also show the possibility that Syô-saiko-tô and Dai-saiko-tô inhibit the injury of aortic endothelial cells. On the other hand, Syô-saiko-tô was reported to inhibit hypercholesterolemia in rats.[3] Antihyperlipidemia[1,2] and antihypertensive action[10] of Dai-saiko-tô were also reported in rats. The difference of their results from ours may be explained by the difference of the animals used. The highest serum cholesterol level in rats fed a 1% cholesterol diet with 0.2% cholic acid was about 200−300 mg/dl serum, while the maximum serum cholesterol level in a rabbit fed a 0.75% cholesterol diet was about 3000 mg/dl serum. The sudden increase of serum cholesterol in rabbits may depress the actions of Syô-saiko-tô and Dai-saiko-tô. Anyway, it is worth noting that Syô-saiko-tô and Dai-saiko-tô at a dose of 0.9 g/kg which is almost equal to 10 times the human dose per day have an anti-atherosclerotic effect as well as soysterol which is 60 times the human dose per day. Our present data indicate that Syô-saiko-tô and Dai-saiko-tô are beneficial for the therapy of atherosclerosis. In this paper, the improvement of Syô-saiko-tô on volume elastic modulus, histopathological findings, and hydroxyproline content was stronger than that of Dai-saiko-tô. These facts show the possibility that the protection of aortic endothelial cells and/or smooth muscle cells by Syô-saiko-tô is stronger than that of Dai-saiko-tô. The difference of the combination of herbal drugs between Syô-saiko-tô and Dai-saiko-tô is attractive. *Panax ginseng* root and *Glycyrrhiza glabra* root are characteristic herbal drugs for Syô-saiko-tô, although the other five composed crude drugs are common to Dai-saiko-tô. The action of *Panaxa ginseng* root and *Glycyrrhiza glabra* root remains to be studied. Their active ingredients should be also clarified.

Acknowledgement

和文抄録

0.75% cholosterol 含有飼料でウサギを 6 カ月間飼育することにより作製した実験的動脈硬化に対する小柴胡湯，大柴胡湯の効果を経口投与により検討した。動脈硬化の指標として最近開発された光学的無侵襲計測を行い，血管弾性特性 (Ev) を経時的に測定した。さらに，血清脂質を経時的に定量した。6 カ月の飼育終了後に胸部大動脈を摘出し，粥状硬化病変面積からの動脈硬化指数の算出，動脈硬化病変の組織学的検討，動脈壁障害の指標として動脈壁中の脂質含量の測定さらに，動脈壁中のコラーゲンの指標として hydroxyproline 含量の測定を行った。結果は，小柴胡湯，大柴胡湯に血管壁弾性特性の cholesterol による上昇抑制が認められた。さらに，動脈硬化指数，胸部大動脈の組織学的所見，胸部大動脈壁中の脂質及び hydroxyproline 含量の cholesterol による悪化あるいは上昇が，両漢方方剤特に小柴胡湯により強く抑制された。しかし，両方剤は，血清 cholesterol の上昇を改善させなかった。これらの結果は，小柴胡湯，大柴胡湯が，高 cholesterol 血症に由来する大動脈内皮細胞障害あるいは平滑筋細胞障害を改善させることを示唆している。

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