# The inhibitory effects of single and combined administration of Sho-saiko-to, Red Ginseng, Keishi-bukuryo-gan and Hochu-ekki-to on thioacetamide-induced liver cirrhosis in rats

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## Abstract

Effects of some Kampo medicines in combinations were investigated using rats with thioacetamide-induced liver cirrhosis. Male rats of Wistar strain were fed thioacetamide-containing diet with either of Sho-saiko-to (小柴胡湯), Red Ginseng, Keishi-bukuryo-gan (桂枝茯苓丸) or Hochu-ekki-to (補中益気湯), individually or in combinations. Increase in serum $\gamma$-globulin by thioacetamide was reduced with administration of Red Ginseng, Sho-saiko-to, especially in combination, along with Keishi-bukuryo-gan plus Sho-saiko-to, Keishi-bukuryo-gan, or Hochu-ekki-to, while the decrease in serum albumin was reduced with either Red Ginseng, Red Ginseng plus Sho-saiko-to, Sho-saiko-to plus Keishi-bukuryo-gan or Sho-saiko-to.

The elevation of serum collagen type IV, 7s domain by thioacetamide, was also reduced by Red Ginseng plus Sho-saiko-to as well as Keishi-bukuryo-gan plus Sho-saiko-to. The improvement in serum GOT, ALP, *etc.* were also noted with these drugs.

The reducing effects of Sho-saiko-to, Keishi-bukuryo-gan, Red Ginseng or Hochu-ekki-to, especially in combinations on histopathological findings using Azan stain in thioacetamide-induced cirrhosis were also observed, consistent with the biochemical parameters.

In conclusion, the reducing effects of some Kampo medicines, especially in conbinations, on thioacetamide-induced rat liver cirrhosis were observed using biochemical and histological parameters.

**Key words** thioacetamide, liver cirrhosis, Kampo medicine, Sho-saiko-to, Keishi-bukuryo-gan, Red Ginseng, Hochu-ekki-to.

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## Introduction

There is a considerable stock of updated knowledge including our data,[1)] concerning the beneficial effects of traditional medicinal plants such as Liquorice, Panax ginseng, Bupleurum falcatum and several traditional Chinese formulae, their composing plants and the active principles. Among them much data has now been compiled about inhibitory actions of saiko-saponins, ginseng saponins, Sho-saiko-to (小柴胡湯) and related formulae in experimental hepatic dam-

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ages and in patients with chronic hepatitis. In addition, authors have reported about the combined effects of some traditional formulae as well as Panax ginseng in experimental and clinical hepatic damages.

There were a few reports about the suppressive actions of Sho-saiko-to to the hepatic fibrotic change induced by some chemicals. The present studies were undertaken to clarify the possible reducing actions of some traditional Chinese formulae including Sho-saiko-to (小柴胡湯), Keishi-bukuryo-gan (桂枝茯苓丸), Hochu-ekki-to (補中益気湯) or Red Ginseng and their combinations on thioacetamide-induced liver cirrhosis in rats using biochemical and histological means.

## Materials and Methods

*Animals* : Male albino rats of the Wistar strain, 3 weeks-old, weighing about 60±2 (S.E.)g, were supplied from Oriental Bioservice Co., Kyoto.

*Thioacetamide treatment* : Thioacetamide, Wako Pure Chemicals Co., Osaka, was solved in water and mixed stepwise with the laboratory chow, Charles River CRF-1 powder, being adjusted to the daily intake of 100 mg/kg body weight. Animals were fed the normal diet and/or thioacetamide for 10 weeks.

*Administration of drugs tested* : Either of Sho-saiko-to (Xiao-Chai-Hu-Tang), Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan) and Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang), in the form of extract granules, was purchased from Tsumura Co., Inc., Tokyo. Korean Red Ginseng powder manufactured by Korea Ginseng and Tobacco Corporation, Seoul, was supplied from Society for Red Ginseng Research, Kobe. Animals received either of the traditional formulae at the daily dose of 1 g/kg body weight, or the Korean Red Ginseng at the daily dose of 0.4 g/kg body weight.

Rats were divided into 8 groups which consisted of the normal diet-fed, the thioacetamide diet-fed and groups fed a diet with either of these traditional formulae, single or in combination in addition to thioacetamide.

*Blood parameters and pathological examinations* : At the end of the experiments, blood was taten by cardiac puncture, under ether anesthesia. Blood chemistry, hematology, electrophoretic patterns of the serum protein and serum collagen type IV, 7s-domain, were determined according to the routine methods. The statistical differences were determined by Student *t*-test. Histological examinations were performed at the blind basis to pathologists. Both routine H.E. stain and Mallory's Azan stain methods were adopted. The collagen fiber was stained blue and the cytoplasm red with Mallory's Azan staining method.

## Results

The body weight at sacrifice was 443±26 (S.E.) g in normal diet-fed group and 247±30 (S.E.)g in

Table I Effects of some traditional Kampo formulae and their combinations on serum GOT levels of thioacetamide-induced liver cirrhotic rats.

| FEEDING | NO. | SERUM GOT IU/l |
|---|---|---|
| A. Normal diet | 5 | 342±17+ |
| B. Thioacetamide diet | | |
| 1) Control | 6 | 438±7 ****vs.A |
| 2) Red Ginseng | 6 | 341±6 ****vs.B-1 |
| 3) Sho-saiko-to | 5 | 435±24 ++vs.B-1 |
| 4) Red Ginseng plus Sho-saiko-to | 6 | 402±16 *vs.B-1 ; **vs.B-3 |
| 5) Keishi-bukuryo-gan | 5 | 447±26 ++vs.B-1 |
| 6) Keishi-bukuryo-gan plus Sho-saiko-to | 6 | 347±24 ****vs.B-1; ****vs.B-3 ; ****vs.B-5 |
| 7) Hochu-ekki-to | 5 | 403±20 ++vs.B-1 |

+Mean±S.E. ++Non-significant
*$p<0.05$ **$p<0.02$ ***$p<0.01$ ****$p<0.001$

thioacetamide diet-fed groups. No significant changes as to body weight among groups administered with traditional formulae.

*Effects of traditional formulae on serum GOT levels in rats with thioacetamide-induced liver cirrhosis (Table I)*

Serum GOT levels were increased in thioacetamide-treated rats, compared with those of normal diet-fed rats. The combined administration of Sho-saiko-to and Red Ginseng as well as Sho-saiko-to plus Keishi-bukuryo-gan, reduced thioacetamide-induced liver cirrhosis. The effect of plain Red Ginseng was also noted.

*Effects of traditional formulae on serum alkaline phosphatase levels in rats with thioacetamide-induced liver cirrhosis (Table II)*

Serum alkaline phosphatase levels were elevated by thioacetamide-diet feeding, whereas either of Sho-saiko-to, Red Ginseng, or Red Ginseng plus Sho-saiko-to, weakened the increasing effect by thioacetamide treatment.

*Effects of traditional formulae on serum protein pat-*

Table II Effects of some traditional Kampo formulae and their combinations on serum alkaline phosphatase (ALP) levels of thioacetamide-induced liver cirrhotic rats.

| FEEDING | NO. | SERUM ALP IU/l |
|---|---|---|
| A. Normal diet | 6 | 418±58+ |
| B. Thioacetamide diet | | |
| 1) Control | 7 | 914±115 ****vs.A |
| 2) Red Ginseng | 6 | 676±63 *vs.B-1 |
| 3) Sho-saiko-to | 7 | 551±27 ****vs.B-1 |
| 4) Red Ginseng plus Sho-saiko-to | 7 | 445±15 ****vs.B-1 ; ****vs.B-2 ; ***vs.B-3 |
| 5) Keishi-bukuryo-gan | 5 | 743±99 ++vs.B-1 |
| 6) Keishi-bukuryo-gan plus Sho-saiko-to | 6 | 732±63 ++vs.B-1 ; ++vs.B-5 |
| 7) Hochu-ekki-to | 5 | 749±18 ++vs.B-1 |

+Mean±S.E. ++Non-significant
*$p<0.05$ **$p<0.02$ ***$p<0.01$ ****$p<0.001$

Table III Effects of some traditional Kampo formulae and their combinations on serum $\gamma$-globulin and albumin levels of thioacetamide-induced liver cirrhotic rats.

| FEEDING | NO. | SERUM $\gamma$-GLOBULIN | SERUM ALBUMIN | ALB/$\gamma$-G |
|---|---|---|---|---|
| A. Normal diet | 6 | 17.4±1.2+ | 58.3±0.4+ | 3.35 |
| B. Thioacetamide diet | | | | |
| 1) Control | 7 | 27.5±2.0****vs.A | 57.0±1.1++ | 2.07 |
| 2) Red Ginseng | 6 | 21.9±0.2****vs.B-1 | 62.1±0.4**** | 2.84 |
| 3) Sho-saiko-to | 7 | 20.9±1.0****vs.B-1 | 59.4±0.4* | 2.84 |
| 4) Red Ginseng plus Sho-saiko-to | 7 | 17.8±1.0****vs.B-1 ****vs.B-2 ;*vs.B-3 | 60.1±0.7** | 3.38 |
| 5) Keishi-bukuryo-gan | 5 | 21.8±1.0***vs.B-1 | 59.4±1.1++ | 2.72 |
| 6) Keishi-bukuryo-gan plus Sho-saiko-to | 6 | 18.6±1.3****vs.B-1 ++vs.B-3 ;*vs.B-5 | 62.1±0.5**** | 3.34 |
| 7) Hochu-ekki-to | 5 | 21.2±1.6***vs.B-1 | 59.8±1.0++ | 2.82 |

+Mean±S.E. ++Non-significant
*$p<0.05$ **$p<0.02$ ***$p<0.01$ ****$p<0.001$

Tavle IV Effects of some traditional Kampo formulae and their combinations on serum collagen type IV, 7s levels of thioacetamide-induced liver cirrhotic rats.

| FEEDING | NO. | SERUM COLLAGEN, TYPE IV, 7s |
|---|---|---|
| A. Normal diet | 6 | 4.70±0.11+ ng/ml |
| B. Thioacetamide diet | | |
| 1) Control | 7 | 5.13±0.16 **vs.A |
| 2) Red Ginseng | 6 | 4.72±0.21 ++vs.B-1 |
| 3) Sho-saiko-to | 7 | 4.81±0.11 ++vs.B-1 |
| 4) Red Ginseng plus Sho-saiko-to | 6 | 4.48±0.10 ****vs.B-1 ; ++vs.B-2 ; **vs.B-3 |
| 5) Keishi-bukuryo-gan | 5 | 4.82±0.14 ++vs.B-1 |
| 6) Keishi-bukuryo-gan plus Sho-saiko-to | 6 | 4.72±0.17 *vs.B-1 ; ++vs.B-3 : ++vs.B-5 |
| 7) Hochu-ekki-to | 5 | 5.02±0.10 ++vs.B-1 |

+Mean±S.E. ++Non-significant
*$p<0.05$ **$p<0.02$ ***$p<0.01$ ****$p<0.001$

*terns in rats with thioacetamide-induced liver cirrhosis (Table III)*

The elevated serum $\gamma$-globulin levels in the thioacetamide diet-fed rats were reduced by the simultaneous administration of either of Sho-saiko-to, Keishi-bukuryo-gan, Red Ginseng or Hochu-ekki-to, more potent in combinations such as Sho-saiko-to plus Red Ginseng or Sho-saiko-to plus Keishi-bukuryo-gan.

The albumin levels were significantly higher in Red Ginseng-administered groups, either single or with Sho-saiko-to combined. As to Sho-saiko-to, the combined administration with Keishi-bukuryo-gan, enhanced its reducing effect on the cirrhotic change.

*Effects of traditional formulae on serum collagen type IV, 7s-domain levels in rats with thioacetamide-induced liver cirrhosis (Table IV)*

The serum collagen type IV, 7s-domain levels were elevated in thioacetamide treatment, while the simultaneous administration of Sho-saiko-to and Red Ginseng, as well as that of Sho-saiko-to and Keishi-bukuryo-gan, reduced the collagen levels to the normal diet-fed levels.

*Effects of traditional formulae on the histological findings of thioacetamide-induced cirrhotic liver (Figures 1-2)*

Thioacetamide treatment led to liver cirrhosis with nodular appearance in the course of 10 weeks which was microscopically shown with characteristic pseudolobular formation as seen in figure 1-A and 2-A. The combined diet with the traditional formulae, strikingly reduced the extent of cirrhotic changes,

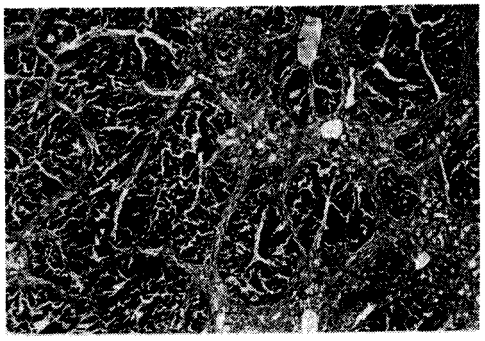

Fig. 1 Effects of traditional Kampo formulae on the histological findings of thioacetamide-induced cirrhotic rat liver (Mallory-Azan stain).
A) Thioacetamide-induced cirrhotic liver.

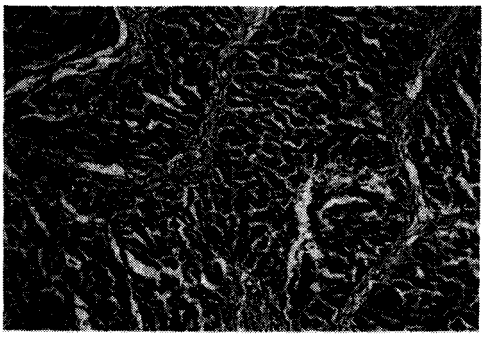

Fig. 2 Effects of traditional Kampo formulae on the histological findings of thioacetamide-induced cirrhotic rat liver (H.E. stain).
A) Thioacetamide-induced cirrhotic liver.

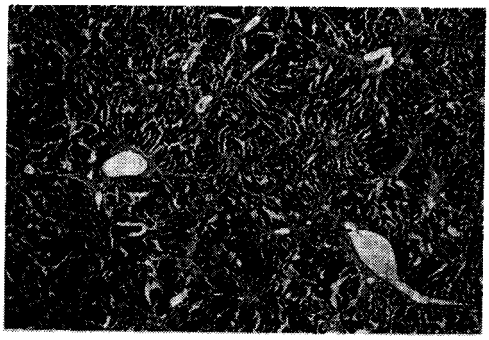

Fig. 1 B) Thioacetamide with Red Ginseng

Fig. 2 B) Thioacetamide with Red Ginseng.

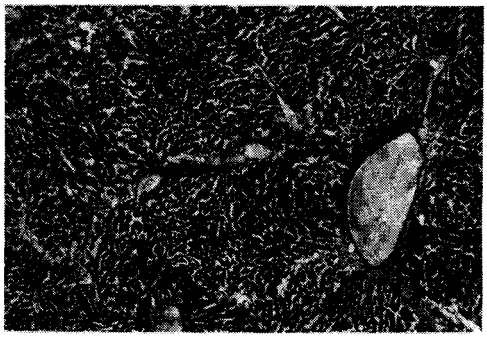

Fig. 1 C) Thioacetamide with Sho-saiko-to.

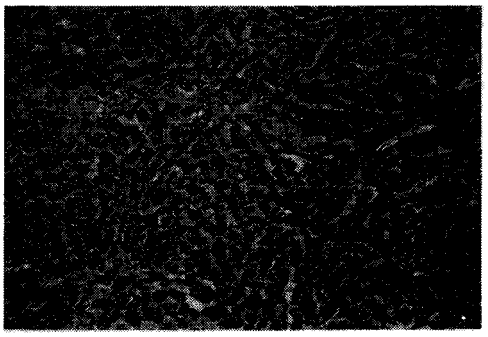

Fig. 2 C) Thioacetamide with Sho-saiko-to.

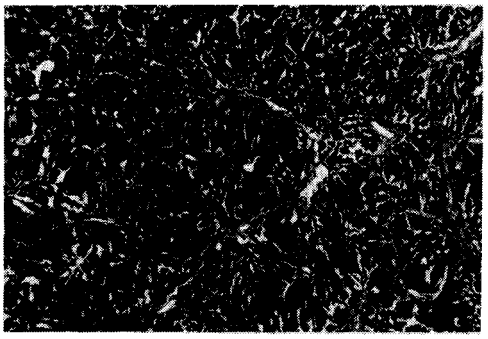

Fig. 1 D) Thioacetamide with Red Ginseng plus Sho-saiko-to.

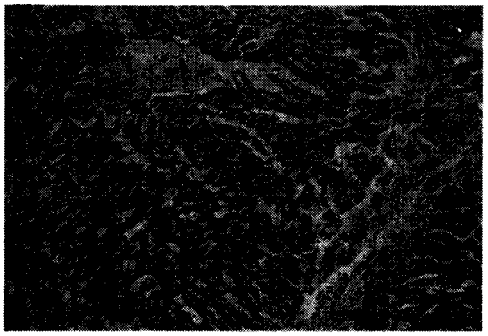

Fig. 2 D) Thioacetamide with Red Ginseng plus Sho-saiko-to.

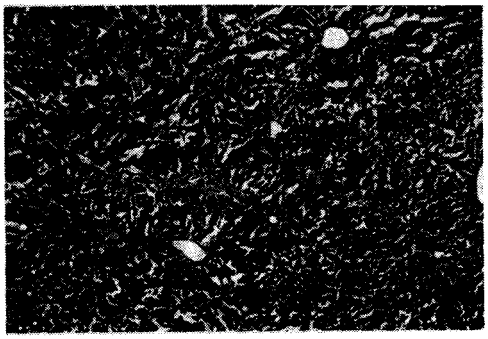

Fig. 1 E) Thioacetamide with Keishi-bukuryo-gan plus Sho-saiko-to.

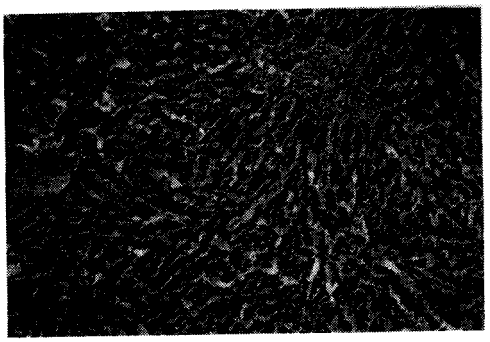

Fig. 2 E) Thioacetamide with Keishi-bukuryo-gan plus Sho-saiko-to.

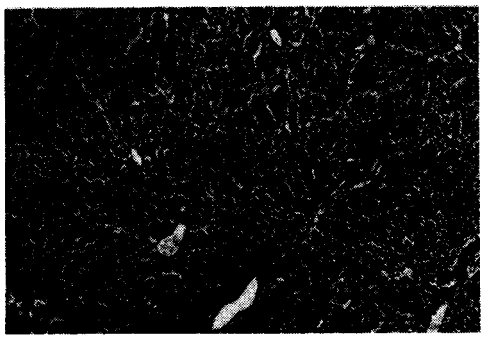

Fig. 1 F) Thioacetamide with Hochu-ekki-to.

Fig. 2 F) Thioacetamide with Hochu-ekki-to.

especially with Sho-saiko-to plus Red Ginseng as well as Sho-saiko-to plus Keishi-bukuryo-gan, consistent with the improvement of biochemical parameters. On Azan stain, the purple stained fibers were abundant with hepatic cell damages and pseudolobules were formed in the liver of the thioacetamide diet-fed rats, while much decrease in fibers and pseudolobule formation with liver cell damage was characterized in rat groups with additional administration of traditional formulae or Red Ginseng.

The other parameters in the blood such as total bilirubin, GPT, total protein, monoamine oxidase (MAO), aminoterminal peptide of procollagen type III (P-III-P), *etc.* remained within statistically non-significant minor changes among groups examined.

## Discussion

In this paper, it was reported that thioacetamide-induced liver cirrhosis in rats was reduced with administration of some traditional Chinese medicinal plants, single or in combinations. Especially the suppressive effects on animals with thioacetamide-induced liver cirrhosis, were found in the cases of administrations of Sho-saiko-to plus Red Ginseng as well as Sho-saiko-to plus Keishi-bukuryo-gan, as detected by biochemical and histological examinations.

Thioacetamide treatment was reported as one of the most reliable and useful experimental methods for studies of liver cirrhosis. Gupta *et al.*[2] administered thioacetamide in the diet, Zimmermann *et al.*[3] in drinking water and Hori *et al.*[4] by the intraperitoneal injection. We adopted thioacetamide-mixed laboratory chow powder at a dosage of 100 mg/kg body weight of the animals. The constant micronodular cirrhosis was obtained by thioacetamide treatment. We used routine blood chemistry data like GOT, ALP as hepatic damage parameters and also serum collagen type IV, 7s or serum protein patterns as liver cirrhotic change parameters along with histological findings by the fibrotic stain method.

Saikosaponins or Sho-saiko-to were reported to be effective in the scute hepatic damage using carbon tetrachloride and D-galactosamine by Abe *et al.*,[5,6] α-naphthyl-isothiocyanate (ANIT) by Yamamoto *et al.*[7,8] or immunological methods such as ADCC, *etc.*.[9,10] The other formulae besides Sho-saiko-to, Keishi-bukuryo-gan and their composing plants showed almost similar effects on ANIT-induced hepatic damage.[8]

It has been reported from our institutions that ginsenosides, Panax ginseng saponins, which had been isolated by Shibata and his colleagues, had the stimulatory actions of DNA synthesis along with cell proliferation of cultured hepatic cells,[11] as well as hepatic RNA, protein [12] and lipid synthesis,[13] DNA, RNA, protein and lipid synthesis in rat bone marrow.[14] Also, saponins from Bupleurum falcatum, saikosaponins named by Takeda and colleagues, were reported by us to have the anti-exudative, antigranulomatous [15] and stimulatory actions of hepatic protein synthesis.[16] The inhibitory effects of ginseng saponins and saikosaponins on the fatty liver of rats were also reported from us along with glycyrrhizin.[17]

The immuno-suppressive and immuno-activating actions of saikosaponins or Sho-saiko-to were clar-

ified by Mizoguchi *et al.*,[18] also the increasing action of interferon by Kagami *et al.*.[19] We have studied increasing action of Sho-saiko-to on IL-8 production in rats.[20] Okita *et al.* also reported that hepatic fibrosis induced by 2-acethylaminofluoren treatment, was reduced with Sho-saiko-to administration.[21]

Among clinical studies. we reported the improving effects of Sho-saiko-to administration *vs.* placebo in patients with chronic hepatitis[7] and did a follow-up study of Sho-saiko-to administration up to 5 years also in patients with chronic hepatitis type C.[22,23] Moreover, the authors showed that the accerelating effect of the Red Ginseng addition to Sho-saiko-to in the course of improvement of chronic hepatitis,[24] in addition to basic data.[25]

The present studies might present fundamental evidence about the effects of some traditional Chinese medicinal plants in prevention and possibly in treatment of liver cirrhosis in man. Judging from these and the previous data, some of traditional medicinal plants including Bupleurum falcatum, Panax ginseng, Glycyrrhizae, *etc.* might prevent or improve the cirrhotic change of the liver through possible hepatic cell-protective, liver cell-proliferative, anti-inflammatory and immunoregulatory actions. The cytokine networks may be associated with the suppressive action of fibrosis in this model. Further study of molecular mechanisms of the action should be elucidated.

In conclusion, the authors demonstrated that experimental micronodular liver cirrhosis in rats fed a thioacetamide-containing diet, was reduced with simultaneous administration in diet with some Kampo medicines, that is, Red ginseng, Sho-saiko-to, Keishi-bukuryo-gan or Hochu-ekki-to, especially in combinations, as detected with serum $\gamma$-globulin, albumin, collagen type IV (7s.), ALP or GOT, along with histopathological findings using Azan stain. The accumulated basis of experimental and clinical data including ours were discussed.

## Acknowledgment

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## 和文抄録

ウイスター系雄ラットをチオアセトアミド含有粉末飼料で10週間飼育すると小結節性肝硬変を生じるが，同時に紅参末，小柴胡湯，桂枝茯苓丸，補中益気湯の単独並びに併用(含有飼料)投与すると肝硬変発生をいかに抑制するかの実験を行った。

その結果，チオアセトアミド投与による血清$\gamma$-グロブリン値の顕著上昇は，小柴胡湯，紅参，桂枝茯苓丸，補中益気湯のいずれか，とりわけ紅参と小柴胡湯併用並びに小柴胡湯と桂枝茯苓丸併用によって著明に抑制された。血清アルブミンは，紅参，小柴胡湯，両者併用，小柴胡湯と桂枝茯苓丸併用によって有意に上昇した。チオアセトアミドによる上昇した血清IV型コラーゲン7s値も，紅参，小柴胡湯併用並びに小柴胡湯，桂枝茯苓丸併用によって有意に低下した。その他チオアセトアミドによる血清GOT，アルカリフォスファターゼ値の上昇も上記薬剤によってほぼ同様の傾向で改善した。

組織学的にはH.E.染色並びに特にマロリーアザン染色像においてチオアセトアミド投与による顕著な偽小葉形成を伴う肝硬変像が，小柴胡湯，紅参，桂枝茯苓丸，補中益気湯それぞれ単独，併用，とりわけ小柴胡湯と紅参併用並びに小柴胡湯と桂枝茯苓丸併用投与によって極めて顕著に抑制されることを示しえた。

本現象の理論的裏付けになると思われる蓄積された実験的並びに臨床的成績につき考察した。

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