

## 간경화 치료에 대한 중국 한의학의 연구 개요

호효평·손창규\*

### Study on Traditional Chinese Medicine against Liver Fibrosis

East-West Cancer Center, Dunsan Oriental Hospital of Daejeon

University, 1136 Dunsan-dong, Seo-gu, Daejeon, 302-122, South Korea

Xiao-Ping Hu, Jang-Woo Shin, Jung-Hyo Cho, Chong-Kwan Cho, Hwa-Seung Yoo, Yeon-Weol

Lee, Chang-Gue Son\*

간섬유화는 다양한 만성 간질환에 기인하는 간실질의 결합조직의 과도한 증식을 말하며, 간경화로 발전하는 중간과정이다. 중국과 한국에는 많은 간섬유화 환자가 있지만 현재까지 서양의학에서 간섬유화를 효과적으로 치료할 수 있는 치료법은 발견되지 않고 있다. 최근 수년간 중국전통의학의 임상과 실험연구에서 많은 발전이 있었다. 전통의학이론을 바탕으로 활혈거어(活血祛瘀), 익기(益氣)의 효능이 있는 한약제가 항섬유화 효능을 보였다. 전통중국의학에서 간섬유화에 대한 일반적인 치료는 유효 성분, 단방 및 복방 처방의 세 부분으로 나뉜다. 우리는 중국전통의학에서 간섬유화의 효과적인 치료와 관련된 작용기작을 소개하였다.

Key Words: Traditional Chinese Medicine (TCM), liver fibrosis, experimental and clinical, prevention and treatment

### Introduction:

High incidence of chronic hepatitis and its related disease in China

According to the Asian Liver Center, 2 billion people of the world have been infected with HBV, and 400 million people of them have chronic infections. On the other hand, China has the greatest burden of chronic infection of HBV and liver cancer. In China, liver fibrosis is the major medical concern because of the high level of hepatitis B viral

infection. Chronic hepatitis B always proceeds as “hepatitis— fibrosis — cirrhosis—sometimes cancer”. In this process, progression to fibrosis or cirrhosis is critical step determining the clinical outcome; prevention against its formation is a most important issue. Accordingly, many countries or pharmaceutical companies have investigated the development of anti-fibrotic or anti-cirrhotic drugs from natural resource. This review aimed to survey and provide information about herbal plant-derived experimental or clinical trials from China to the Korean oriental doctors or scientists working in this field.

\* 대전대학교 한의과대학 간계내과학교실  
· 교신저자 : 손창규 · E-mail : ckson@dju.ac.kr  
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Single component from traditional Chinese medicine

Tetrandrine (Tet) : Tetrandrine (Tet) is the main alkaloid isolated from the lumpy root of *Stephania tetrandra* S. Moor (漢防己甲素). Its molecular formula is  $C_{33}H_{42}N_2O_6$  and its chemical structure belongs to a dibenzyloisoquinidine [1]. Modern pharmacological studies have proved that Tet is a  $Ca^{2+}$  antagonist, which acts mainly on the calcium channel of cell to block the cross-membrane transportation of calcium ions as well as their intracellular distribution and utilization. In recent years, the actions of Tet in preventing and treating hepatofibrosis have gradually attracted attention of more investigators. With the establishment of the technique of liver cell isolation and culture, and advance in technology of molecular biology, studies on the anti-hepatofibrotic effects of Tet have probed into the cellular, subcellular and molecular levels [1]. In clinical study, 115 cases of chronic liver disease treated with oral Tet for 6 months, their serum hyaluronic acid (HA) and procollagen III peptide (PIIIP) levels were remarkably lower than those before treatment ( $P < 0.01$ ). Among them, liver fibrosis disappeared in 14 (15.4%) cases, much reduced in 54 (58.1%) cases and slightly reduced in 19 (20.4%) cases. In addition, there were reductions in inflammatory cell infiltration and the number of Ito cells in the Tet treated patients, as compared with the glucurone controls ( $P < 0.001$ ) [2]. Recently, in order to have a better understanding its hepatoprotective and antifibrotic effects, whole-cell patch-clamp technique was used to observe the effects of Tet on Calcium release-activated calcium

current in rat hepatocytes. Tet could reduce liver cell damage and fibroses, and lower the serum ALT, alkaline phosphatase (ALP) and total bilirubin (TB) [3]. So Tetrandrine is one of the effective component in traditional Chinese medicine.

Kwoninone : Kwoninone, a alkaloid isolated from *Sophora Subpsostarata* (苦蔘素). have the anti-inflammation, antibacterial, antivirus, potential immunomodulating, anticarcinoma and multiple bioactivities. The kwoninone significantly inhibited fibroblastic proliferation, growth and expression of TGF- $\beta$  [4]. In rat model induced by CCl<sub>4</sub> for 10 weeks, serum ALT, AST, TBA, and GGT are reduced in pretreated and post-treated kwoninone groups ( $P < 0.05$ ,  $P < 0.01$ ). And the protein expression of MMP-2 was evident lower than control group ( $P < 0.05$ ,  $P < 0.01$ ) [5]. By the clinical study that efficacy of kwoninone in the treatment of hepatic fibrosis with hepatitis B virus, serum of laminin (LN), HA, PIIIP, type IV collagen (IV-C) have the remarkable difference in the patients of liver fibrosis between treatment with kwoninone before and after. The rate of seronegative for HBsAg, HbeAg and HBV-DNA were 3.3%, 22.8% and 20.0% respectively [6].

Salvianolic acid B (SalB): Salvianolic acid-B (SalB) is one of the water-soluble components isolated from *Salviae Miltiorrhizae Radix* (丹蔘). SalB had strong anti-oxidant activity and could inhibit the fibrilformation [7]. Salvianolic acid B protected the tetrachloride carbon (CCl<sub>4</sub>)-induced fibrosis in rats, and reversed dimethylnitrosamine (DMN)-induced liver fibrosis in rats. It could prevent liver cell injury, and inhibit proliferation of hepatic

stellate cells (HSC) and collagen production in vitro. [8-12]. SalB could inhibit A-beta aggregation and fibril formation, as well as directly inhibit the cellular toxicity of aged A-beta towards PC12 cells [13]. In clinical study compared with the IFN-gamma group, four serological fibrotic markers significant improved and score of liver ultrasound imaging was lower in SalB group. IFN-gamma showed certain side effects (fever and transient decrease of leukocytes, occurrence rates were 50 % and 3.23 %), but SalB showed no side effects [14]. From these study, we known that SalB is one of the effective component for inhibition the fibril formation and has no side-effect.

Other single component widely used in China : Amygdalin, Schisandra sphenanthera, Cucurbitacin B, Oleanolic acid etc, have been proved to have the active effect on anti-fibrosis.

Single description of traditional Chinese medicine

Danshen (*Salvia Miltiorrhizae Radix*) (丹参): Danshen is the root of *Salvia miltiorrhiza*. Danshen has been used infrequently in ancient Chinese medicine. Yet it has become an important herb in modern Chinese clinical practice. Danshen inhibited ET-1-induced depletion of intracellular calcium, which had no correlations with the influx of extracellular calcium. Danshen also inhibited KCl-induced influx of calcium, indicating its characteristic of blocking voltage-operated Ca<sup>2+</sup> channel [15]. In another study, Danshen decreased [Ca<sup>2+</sup>] in activated HSCs, which may be one of important ways to block liver fibrosis [16].

There were dose- and time-effective relationships of Danshen on anti-lipid peroxidation of mitochondria of hepatic fibrosis in rats. Danshen improved liver tissue injuries and reduced the magnitude of fibrosis in rats with CCl<sub>4</sub> and DMN (dimethylnitrosamine)-induced hepatic fibrosis [17]. Danshen decreased the hypoxanthine and MDA (malondialdehyde) levels in the liver tissue [18]. Danshen appears a marked hepatoprotective effect and with few side-effects. Based on the traditional medical theory, hepatoprotective function of Danshen as above could be interpreted due to its effect at improving blood circulation and promoting regeneration of liver cells.

*Astragali Radix* (Root *Astragali*; Huang Qi) (黄芪): *Astragali Radix* is the dried root of *Astragalus membranaceus* (Fisch.) Bunge (膜莢黄芪) and *Astragalus mongholicus* Bunge (Fabaceae) (蒙古黄芪); family Leguminosae(豆科). It is mainly produced in inner Mongolia, Shanxi, Gansu and Heilongjiang provinces of China [19]. Primarily, the active constituents of *Astragali Radix* consist of polysaccharides and flavonoids [20]. *Astragalus membranaceus* (AM) has been widely used for treating liver diseases in traditional Chinese medicine. The effect of AM of on hepatocarcinogenesis induced by diethylnitrosamine(DEN), two-thirds partial hepatectomy, and 2-acetylaminofluorene (2-AAF) (DEN-PH-AAF) was evaluated using glutathione S-transferase placenta form (GST-P) as marker. The formation of GST-P-positive foci and the expression of GST-P protein and mRNA caused by DEN-PH-AAF were reduced in the treatment groups, which clearly suggests that AM is effective in delaying DEN-PH-AAF-induced

hepatocarcinogenesis [21]. Astragalus injection on CCl<sub>4</sub>-ethanol-induced hepatic fibrosis remarkably decreased serum HA and LN levels ( $P < 0.05$ ) and liver MDA level ( $P < 0.01$ ), but increased the activity of liver SOD ( $P < 0.01$ ). Astragalus injection also decreased fibrosis formation and expression of LN. The mechanism is possibly associated with the action of antioxidant and the expression of decreasing LN [22]. The change of fibrogenesis serum markers before and after astragalus injection in patients with chronic hepatitis, in astragalus injection patients, TGF- $\beta$ 1, HA is high in serum compared with the control group. Astragalus injection have the effect of decrease the fibrogenesis serum markers on the patients of chronic hepatitis [23].

Semen Persicae (Taoren) (桃仁): Taoren is the seed of *Prunus davidiana* Subovoid, smaller but thicker, about 0.9 cm long, 0.7 cm wide and 0.5 cm thick. TaoRen extract can significantly counteract hepatic fibrosis caused by CCl<sub>4</sub> by promoting the dissolution of collagen as well as of fibronectin. Taoren can significantly reduce the formation of fibrous septa composed of collagenous fibers and reticular fibers, thus stimulating the recovery of hepatic tissues [24]. Taoren has suppressive effects on fibroblast growth in in-vitro cell cultivation. Furthermore, it can suppress the proliferation of inflammatory cells and fibroblast hyperplasia in subjects of experimental trabeculae dissection [25]. Taoren acted on hepatic fibrosis induced by CCl<sub>4</sub>, through promoting the degradation of collagens type I, II, IV, VI and fibronectin. Taoren has proved helpful in markedly reducing the fibrous septa composed of both

collagenous and reticular fibers as well as in repairing the structure of hepatic tissues [26]. Taoren is one of the safe and effective traditional medicine for inhibition the liver fibrosis.

Cordyceps Sinensis (Dongchongxiacao) (冬蟲夏草): Cordyceps Sinensis is a well-known plant that has been used in traditional Chinese medicine to restore energy, promote longevity, stimulate the immune system, and to improve quality of life. Ancient records claim that it is beneficial for the heart, circulatory system, liver, kidneys, respiratory system, and sex organs in TCM. An interesting study was done in China, where 70 patients with chronic hepatitis B and post hepatic cirrhosis were treated either with Cordyceps or with another herbal combination of proven effectiveness against liver disease, whose main ingredient was the medicinal Mushroom *Ganoderma applanatum*. A significant clinical response was seen in 68% of the Cordyceps patients and in 57% of the *Ganoderma* patients. Result shows Cordyceps is a bit better at treating this type of liver disease than is the *Ganoderma applanatum*, which is a type of Reishi [27]. Another study on the effects of cordyceps sinensis and its mechanism in liver fibrosis, colchicine was used as control therapy. They were both able to markedly reduce serum PC III level, and reduce I, III, IV collagen deposition in liver tissue, and then prevent the formation of pseudo-lobule and cirrhosis. Both Cordyceps sinensis and colchicine had satisfactory effect on hepatic fibrosis. They can inhibit proliferation and transition of hepatic fat-storing cells (desmin-positive cells), so as to reduce collagen synthesis and deposition in

liver. *Cordyceps sinensis* is a useful anti-fibrotic drug in chronic liver diseases also has no side-effect whereas colchicine always has some side-effect [28].

Other single description widely used in China: Traditional Chinese herbs activating blood circulation to dissipate blood stasis such as *Angelica sinensis* (DangGui 當歸), *Ligusticum chuanxiong* (川芎), *Red Peony Root* (ChiShao 赤芍藥), *Safflower* (HongHua 紅花), *Rhizoma Sparganii* (SanLeng 三棱) and *Curcuma phaeocaulis* Valeton (EZHU 莪朮), have the effect of anti-fibrosis. Also, according to a theory of Liver-discharging and Qi-regulating formulae (疎肝理氣), *Bupleurum chinense* DC. (ChaiHu 柴胡), *Glycyrrhiza uralensis* Fisch (GanCao 甘草), *Poria cocos* (Schw.) (FuLing 茯苓) and *Magnolia officinalis* Rehd. et Wils (HouPu 厚樸) have effects for liver fibrosis, as well widely used in China.

Multiple compound of traditional Chinese medicine

FuFangBieJiaRuanGanPian (復方鱉甲軟肝片) (FFBJRGP): FuFangBieJiaRuanGanPian is a multiple description developed by BeiJing302 Hospital according to the traditional Chinese theory and a long-term clinical and experimental experience. It is composed of *Carapax Trionycis* (Biejia), *Paeonia veitchii* Lynch (ChiShao), *Cordyceps Sinensis* (Dongchongxiacao), *Radix Isatidis* (BanLanGen) and otherwise traditional Chinese medicine [29]. To study the effect of the FFBJRGP in an experimental model of hepatic fibrosis and its pharmacodynamics, hepatic fibrosis induced by carbon tetrachloride in rat

were given by FFBJRGP as high, moderate, and low dosage respectively. The results showed the reduction in TIMP-1 and TIMP-2, obviously up-regulated expression of MMPs in protein and mRNA levels, and suppression of SC and TGF- $\alpha$  expression comparing to control group. ECM degradation was generally parallel to the changes in MMPs [30]. For clinical evaluation of the chronic hepatitis B with liver fibrosis, the parameters of fibrosis level such as hyaluronic acid (HA), laminin (LN), collagen IV were observed. 96 patients with abnormal parameters of fibrosis level were randomly divided into two groups. 48 patients were treated by FFBJRGP and the control group treated by Fufandanshengpian. The parameters of fibrosis level such as HA, LN, IV-C were greatly improved in treatment group ( $P < 0.01$ ), and liver function was improved in treatment group ( $P < 0.05$ ) [31]. The results suggested that FFBJRGP might affect several key steps in the process of hepatic fibrosis and possess multi-drug effects for treatment of liver fibrosis.

Fuzhenghuayufang (扶正化癆方): Fuzhenghuayu decoction, also called as 319 decoction, is composed of *Radix salviae miltiorrhizae*, *Cordyceps sinensis*, *Semen persicae*, etc. From the study to investigate the effect of Fuzhenghuayu decoction (solution of herb extract concentration of 0.04g/ml) on autocrine activation of hepatic stellate cell (HSC), the drug-serum inhibited VEGF secretion from activated HSC and activation of HSC. Fuzhenghuayu decoction acts effectively against the autocrine activation pathway of HSC. The mechanism may be associated with the inhibition of the secretion of VEGF by

activated HSC [32]. In experimental study, Fuzhenghuayufang could inhibit tumor growth in vivo, and resist hepatic fibrosis and striking increase of TGF- $\beta$ II $\alpha$  expression [33].

Fufangdanshen (861chongji): Compound 861 is made of total 10 herbs including HuangQi(Root Astragali), DanShen(Salvia Miltiorrhizae), JiXueTeng(Caulis Spatholobi) and Salvia miltiorrhiza as its chief component. Compound 861 has been shown experimentally to be effective in suppressing fibrogenesis, enhancing collagen degradation, and inhibiting TIMP expression. The antifibrotic mechanism due to decreases the mRNA level of MMP-2, but transiently increases the enzymatic activities of MMP-2. Compound 861 may be mediated by decreasing TIMPs, the inhibitors of MMPs, during resolution stage of fibrosis. This is probably one of the mechanisms where by herbal Cpd 861 exerted its antifibrotic action in this experiment [34]. The compound 861 showed the therapeutic effect on cell proliferation in human hepatic stellate cells (LX-2) and human hepatocellular liver carcinoma cells(HepG2), and expression of alpha-smooth muscle actin(alpha-SMA) in LX-2 cells. Since hepatic cell proliferation and high level of alpha-SMA are associated with liver fibrosis, Cpd 861 may be a useful candidate in treatment of liver disease [35].

Other multiple compound of traditional Chinese medicine: Xuefuzhuyutang 血府逐瘀湯 (DangGui當歸, ChuanXiong川芎, ChiShao赤芍藥, TaoRen桃仁 and HongHua紅花, etc.); Minor bupleurum decoction (also named XiaoChaiHuTang小柴胡湯: ChaiHu柴胡, HuangQin黃芩, BanXia半夏, ShengJiang生姜, RenShen人蔘, GanCao甘草, DaZao大棗);

TaoHongSiWuTang 桃紅四物湯 (TaoRen桃仁, HongHua紅花, DangGui當歸, ChuanXiong川芎, ShengDi 生地黃, BaiShao白芍藥); Qi-shu-ke-li (氣舒顆粒) (Guang An Men Hospital, BeiJing,China Academy of Chinese Medical Sciences, developed the compound “Qi-shu-ke-li”, have a clinical treatment history about 20 years). Above these compound of traditional Chinese medicine widely used in therapy of liver fibrosis and proved an clinical efficacy in China.

#### Discussion and conclusion

Liver fibrosis, the common and basic pathological change of all kinds of chronic hepatic disease, is the early stage of hepatic cirrhosis. The fibrogenic process is dynamic, and is a serious but reversible consequence. China and Korea has a high incidence of hepatic injury and fibrosis, but current therapeutic options remain inadequate. Until now, specific, effective, safe and cheap antifibrotic therapies are yet lacking, so to develop the effective therapies is most urgent. In near future, targeting of stellate cells, gene therapy, cytokine antagonist, and fibrogenic mediators will be a mainstay of antifibrotic therapy. The advantage of TCM therapy due to traditional herb medicines have effective multi-component, so as to widely action with many targets, and have less side effects.

As shown above examples, oriental medicine in China and Korea has a numerous herb-derived hepatotherapeutic medicines based on long historical practical experience and countless kinds of medical plants. General concept of oriental medical pharmacology has suggested that the herbs with activities of

“activating blood circulation to dissipate blood stasis, and supporting the healthy energy” could be a potential for anti-fibrosis [36]. However, majority of studies was showed in experiment and minority in clinic by present. In the future, new study work may be able to progress in experimental research at even genomic level and well-designed clinical trial.

The natural resource-derived single compounds, extracts or prescriptions with putative anti-fibrotic activity have gained increasing attention in worldwide pharmaceutical industries. It is expected that this review of anti-fibrotic therapeutics in China should give us useful information for treatment or drug development of liver fibrosis and cirrhosis.

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