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Traditional Chinese Medicine (TCM) for fibrotic liver disease: Hope and Hype

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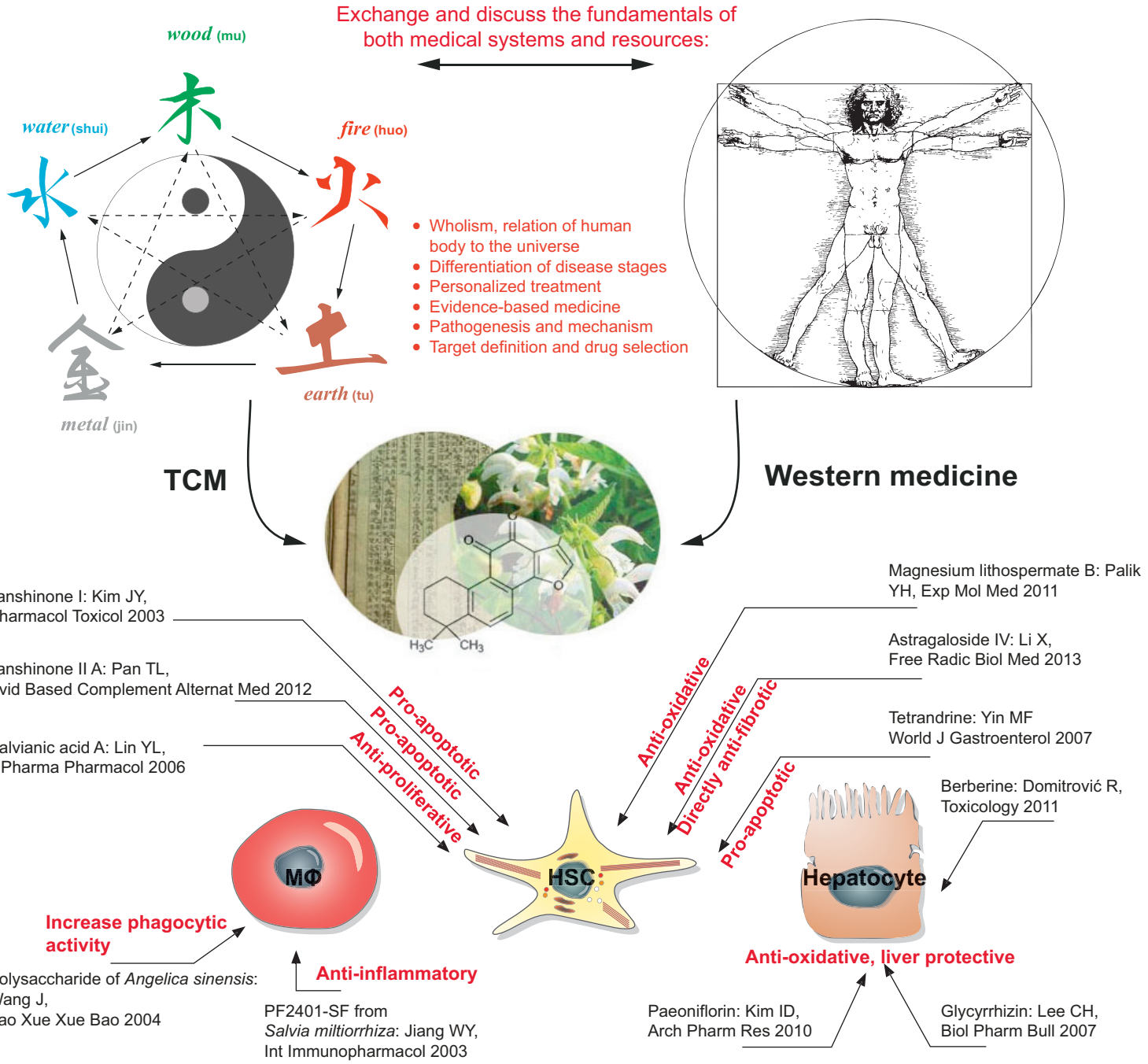

Fig. 1. The possibility of translating traditional Chinese medicine (TCM) into therapy of chronic liver diseases (CLD). The merger of holistic TCM with the more particularistic and complementary views of Western medicine holds promise for the development of novel drugs for CLD including liver fibrosis. Implementation of cutting-edge technologies and rigorous study design should finally create innovation and synergism. Shown are examples of TCM drugs and their cellular activities relevant for liver inflammation and fibrosis. Implementation of cutting-edge technologies and rigorous study design should finally create innovation and synergism. MΦ: macrophage; HSC, hepatic stellate cell; HEP, hepatocyte.

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Table 1. Clinical studies on the efficacy of TCM in the treatment of CLD.

Formulas	Patients (trial design)	Diseases	Duration (wk)	Parameters improved	Reference
Compound 861	102 (RC)	Early stages of cirrhosis, liver fibrosis with CHB	24	Liver function, serum fibrosis markers, inflammatory and necrosis grade	Yin SS, *et al.*, Chin J Hepatol 2004
Biejiaruangan compound	104 (RC)	Cirrhosis with CHB	24	Serum fibrosis markers, size of portal vein and spleen	Gao GF, *et al.*, Chin J Clin Hepatol 2006
Fuzhenghuayu capsule	216 (RC)	Liver fibrosis with CHB	24	Liver function, serum fibrosis markers, inflammatory grade	Liu P, *et al.*, World J Gastroenterol 2005
Qiang gan ruan jian Tang	38	Cirrhosis with CHB, and/or CHC	12	Liver function, ascites levels, symptoms of cirrhosis	Wang ZW. J Military Sur Southwest China 2009
Qiang gan ruan jian Fang	62 (RC)	Cirrhosis with CHB and/or schistosomiasis	12	Serum fibrosis markers, size of portal and splenic vein	Wang XS, *et al.*, Shanghai J Tradit Chin Med 2003
Qiang gan ruan jian Wan	70 (RC)	Cirrhosis with CHB and splenomegaly	5	Liver function, size of portal vein and spleen	Shi HL, *et al.*, Jilin J Tradit Chin Med 2006
Qianggan capsule	88 (RC)	Non-alcoholic fatty liver disease	24	Liver function, serum TG level, liver/spleen ratio	Li L, *et al.*, Chin J Integr Med 2010
Qianggan capsule	63 (RC)	Liver fibrosis with CHB	24	Serum fibrosis markers, inflammation and necrosis	Yang LM, *et al.*, Chin J Integr Med 2002
Qianggan capsule	60	Non-alcoholic fatty liver disease	12	Liver function, serum TC, TG, HDL-C levels, liver/spleen ratio	Zhang W, *et al.*, Shanghai J Tradit Chin Med 2007
Qianggan capsule	80 (RC)	Liver fibrosis with CHB	16	Liver function, serum fibrosis markers	Xue GQ, *et al.*, Shandong J Tradit Chin Med 2004
Yi gan kang	365 (RC)	Liver fibrosis with CHB	24	Serum fibrosis markers, liver function, size of liver and spleen	Yao HS, *et al.*, Clin Focus 2009
Yi gan kang	116 (RC)	CHB	16-24	Liver function, percussion tenderness, HBeAg and/or HBV-DNA	Jia SY, *et al.*, Chin Remedies & Clinics 2007
Yi gan kang	180 (RC)	CHB	24	Liver function, percussion tenderness, size of liver and spleen, HBV-DNA, HBeAg, HBsAg	Han FY, *et al.*, Chin Cummunity Doctors 2012
Jian pi bu shen Fang	50 (RC)	Cirrhosis complicated by hepatorenal syndrome	3	Liver function, renal function	Tang G, *et al.*, Mod Tradit Chin Med 2013

Only the 3 major ingredients are listed. Compound 861: *Salvia miltiorrhiza, Radix Astragali, Cordyceps*; Biejiaruangan Compound: *Carapax trionycis, Panax pseudoginseng, Radix Paeoniae Rubra*; Fuzhenghuayu Capsule: *Salviae miltiorrhizae, Cordyceps, Semen Persicae*; Qiang gan ruan jian Tang: *Salvia miltiorrhiza, Radix Astragali, Carapax trionycis*; Qiang gan ruan jian Fang: *Codonopsis pilosula, Angelica sinensis, Carapax trionycis*; Qiang gan ruan jian Wan: *Radix Astragali, Carapax trionycis, Manis pentadactyla;* Qianggan Capsule: *Salvia miltiorrhiza, Radix Astragali, Codonopsis pilosula;* Yi gan kang: *Angelica sinensis, Radix Astragali, Salvia miltiorrhiza*; Jian pi bu shen Fang: *Radix Astragali, Salvia miltiorrhiza, Atractylodes macrocephala*.
RC, randomized controlled; CHB, chronic hepatitis B; CHC, chronic hepatitis C; TG, triglycerides; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol.

Therapies that specifically retard progression or induce regression of fibrotic liver disease have entered the clinical stage [1,2]. This is remarkable, since clinical validation of antifibrotic efficacy remains difficult and since the mere reduction of excess scarring, without an improvement of hepatic angio-architecture and synthetic function is a disputed primary clinical endpoint [3]. Importantly, as in cancer therapies, drugs that address more than a single pathogenic pathway are usually more efficient than single highly specific pathway modulators [1]. Moreover, the high costs and risks of drug development have opened the field for drug repurposing, i.e., the validation and use of defined agents that were already tested clinically for diseases other than fibrosis. These insights have further sparked an interest in a more holistic pharmacological approach to fibrosis, which includes reevaluation of the herbs of Traditional Chinese Medicine (TCM).

The recorded history of TCM can be traced back over 2000 years, although it is common belief that its origins range as far back as Chinese civilization, i.e., >5000 years. TCM derived its theoretical foundations, including diagnostic and treatment methodologies, from ancient Chinese philosophy. It virtually dragged the Chinese nation through periods of poverty and chaos as an exclusive medical way of health care, before Western medicine was introduced after a series of revolutionary campaigns in the 20th century.

Unlike Western medicine, TCM strictly relies on the two therapeutic pillars of holism and syndrome differentiation. In this system, the human body is not simply regarded as an entity in which different parts work interdependently but also a portion of the universe in which it is embedded and with which it interacts. Sickness is triggered by the imbalance of Yin and Yang, a concept of contrary but complementary forces in nature, resulting in various symptoms with a dynamic trend in the course of disease. Here, holistic but individualized approaches that use herbal remedies are targeted at the complex syndrome, to help the body regain balance and harmony.

Chronic liver diseases (CLD) have never been described as such in written documentations of TCM. Therefore, it has been difficult to establish a precise description of CLD in modern TCM, and symptomatic terms such as abdominal swelling, yellow skin and right upper abdominal pain were included only in the 1970s [4]. Thereafter, the definition of CLD in TCM was gradually refined to encompass: (1) Weakening of the Qi (biological substances/activities that preserve life); (2) blockage of meridians (circulation channels of Qi) by blood stasis; (3) generation of dampness and heat (inflammatory pathogens) [5]. Only then studies began to systematically examine the effect of TCM on defined CLD [6]. Major aims were the eradication or suppression of the underlying cause of CLD, such as HBV or HCV infection, and treatment of its hard endpoints, cirrhosis and HCC, with a major focus on fibrosis. However, there remained problems to reconcile TCM, which traditionally valued empiricism and holistic philosophy, with the Western approach to CLD, such as a reproducible standardization of herbs using quantifiable lead compounds (biologically active ingredients), the frequent lack of rigorous stratification of patients or absence of a double-blind, randomized, placebo-controlled clinical trial design. Moreover, mechanistic preclinical validation of TCM drugs is still in its infancy, with a focus on select cultures of liver cells and cell lines, and a relatively narrow spectrum of *in vivo* rodent models of liver inflammation and fibrosis. Finally, some TCM drugs have been accused of negligent safety evaluation, based on case reports of hepatotoxicity or nephrotoxicity [7], largely due to contamination with heavy metals or toxic alkaloids. However, the Chinese government has begun to initiate a national safety plan in 2011, investing in the modernization of TCM ($100 million from the National Natural Science Foundation in 2012), to promote research on lead compound identification and mechanisms of action, on a better standardization and well controlled clinical trials.

Thus numerous clinical trials, some of them NIH-registered, were initiated and several formulations received approval by the China Food and Drug Administration. Approved and broadly marketed anti-fibrotic formulations are: Compound 861, an aqueous extract of 10 herbs targeting blood stasis and liver stagnation [8]; Biejiaruangan Compound (CBJRGC), a prescription containing *Carapax trionycis* (turtle shell) and 10 herbs to soften the liver [9]; Fuzheng Huayu (FZHY), consisting of six herbs, to resolve blood stasis and nourish the liver [10]. Both CBJRBC and FZHY reached sales >$30 million

during 2012 in China, and an antifibrotic effect of FZHY has been suggested in a recently completed US FDA-approved trial in patients with chronic hepatitis C [11]. Table 1 lists major published studies on TCM for the treatment of liver fibrosis.

Predictably, TCM should provide a rich resource for developing anti-inflammatory, anti-infectious, and anti-fibrotic drug candidates. A major challenge is its reconciliation with Western medicine, requiring translation of the TCM codes into a more scientific language, and identification of effective lead compounds in the heterogeneous herbal mixtures or extracts. The latter has already been achieved in some cases, revealing, e.g., interesting plant-derived polyphenols, flavonoids or alkaloids that serve as antivirals, antioxidants or anti-fibrotics, often affecting different liver cells and signaling pathways (Fig. 1). However, identification of single active components partly contradicts the holistic theory of TCM which postulates that active ingredients and herbs will not work in isolation, a paradigm that reemerges even in Western medicine. An example is the appreciation of, e.g., the combined effect of nutrition, the intestinal microbiome, and physical exercise on metabolic, liver, and cardiovascular health [12]. Nonetheless, a valid compromise is to test individual compounds in isolation and then recombine agents with proven efficacy.

Controversies how to further develop TCM are ongoing in China. One group deplores the modernization of TCM as submission to Western rules, the other group demands its continuing overhaul. There is also a concern of deteriorating drug quality, including contaminants accumulating in cultured herbs. Moreover, many young practitioners feel that adherence to TCM will compromise their career, and patients, especially in the cities, are increasingly skeptical about the efficacy of TCM. Still there is an overwhelming consensus that implementation of methodological improvements and rigorous scientific testing along the principles of evidence-based medicine will help to exploit the vast potential of TCM.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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