



Anti-fibro-hepatocarcinogenic Chinese herbal medicines: A mechanistic overview

Alex Boye^{1,2}, Yan Yang², James Asenso³, Wei Wei³

ABSTRACT

Chinese herbal medicine (CHM) is an integral component of complementary/alternative medicine and it is increasingly becoming the preferred therapeutic modality for the treatment of liver fibrosis and hepatocellular carcinoma (HCC) worldwide. Accordingly, the World Health Organization (WHO) has attested to the popularity and efficacy of indigenous herbal therapies including CHM as a first line of treatment for some diseases including liver disorders. However, the WHO and drug discovery experts have always recommended that use of indigenous herbal remedies must go hand-in-hand with the requisite mechanistic elucidation so as to constitute a system of verification of efficacy within the ethnobotanical context of use. Although many CHM experts have advanced knowledge on CHM, nonetheless, more enlightenment is needed, particularly mechanisms of action of CHMs on fibro-hepato-carcinogenesis. We, herein, provide in-depth mechanisms of the action of CHMs which have demonstrated anti-fibro-hepatocarcinogenic effects, in pre-clinical and clinical studies as published in PubMed and other major scientific databases. Specifically, the review brings out the important signaling pathways, and their downstream targets which are modulated at multi-level by various anti-fibro-hepatocarcinogenic CHMs.

¹Department of Medical Laboratory Science, School of Allied Health Sciences, College of Health and Allied Sciences, University of Cape Coast, Cape Coast, Ghana, ²Department of Pharmacology, Institute of Natural Medicine, Anhui Medical University, Hefei, Anhui Province, China, ³Institute of Clinical Pharmacology, Anhui Medical University, Hefei, China

Address for correspondence:

Alex Boye, Department of Medical Laboratory Science, School of Allied Health Sciences, College of Health and Allied Sciences, University of Cape Coast, Cape Coast, Ghana.
E-mail: boye_alex@yahoo.com

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INTRODUCTION

Chinese herbal medicine (CHM) that forms an integral component of traditional Chinese medicine (TCM) keeps growing popular worldwide [1,2]. The past few decades have seen increased scientific investigations on commonly used CHMs often reflective of the ethnobotanical context, in which they are used. As a result, it is common to find scientific studies on whole Chinese herbal formulas, whereby the pharmacological and therapeutic effects more often are attributed to the entire components of the herbal formula. This has always been the source of criticism of CHM therapy just like other indigenous herbal remedies, especially from strict adherents of western medicine. There has been a paradigm shift in recent years with regards to research on CHMs which have seen an incredible focus on mechanistic elucidation as well as structural and

functional characterization of individual components of CHMs. Many scientific efforts have been made to highlight the mechanisms of the action of CHMs [3], but there is still more work to be done. Hepatitis B virus (HBV) endemicity correlates with the incidence of liver fibrosis and its attendant complications including cirrhosis and hepatocellular carcinoma (HCC). China is noted for a high incidence of HBV infections and alcohol abuse [4]. Coincidentally, these two factors are crucial risk factors for HCC [4]. Almost 80-90% of HBV-related HCC in Asia and Africa occur in China [5,6]. Although, many scientific efforts have been made to highlight the mechanism of action of CHMs [3] used in the treatment of hepatocarcinogenic disorders, nonetheless the mechanistic elucidation of CHMs remains incomplete. This review provides a mechanistic overview of CHMs which have demonstrated *in vitro* and *in vivo* anti-liver fibrosis, anti-cirrhosis, and anti-HCC effects featured

in published scientific articles from PubMed and other major scientific databases. Specifically, it highlights the mechanisms of the action of CHMs in the light of specific therapeutic targets that can be explored in future studies.

CHM

CHM is an integral component of TCM. CHM has multi-compound composition, multi-modulatory, and multi-target action [1] [Figure 1]. It produces less adverse effects in the treatment of liver diseases [7-9]. In CHM practice, liver disease is assumed to be caused by a number of factors including poor blood circulation and dysregulated metabolism [10]. Thus, CHM therapy against liver disease is solely to reduce blood stagnation, eliminate toxins and improve the immune system. CHM practice involves the use of either one herb/plant extract or a mixture of two or more herbal extracts based on a time-tested system of herbology. According to the principles and theories governing CHM practice, one pharmacologically active compound from one of the constituent herbs is normally regarded as “King herb” [11]. The “King herb” is the main medicine which exerts the expected therapeutic action. To enhance the therapeutic action of the “King herb,” the other component herbs play auxiliary functions, such as enhancing delivery of the “King herb” to target site, reduce toxicity/side effects of the “King herb,” and most importantly, provide synergistic effect to the “King herb.”

PATHOGENESIS OF FIBRO-HEPATO-CARCINOGENESIS

Fibro-hepato-carcinogenesis epitomizes a spectrum of pathological events in the liver manifesting as liver fibrosis, cirrhosis and HCC if not treated at the initial stages. The whole pathological process begins as a result of dysregulated wound healing process secondary to chronic hepatic inflammation. Hepatic stellate cell (HSC) is the key hepatic cell implicated in liver fibrosis. Under normal physiological conditions, quiescent ito cells store retinoids (vitamin A) and play crucial homeostatic roles in the liver. However, in response to chronic inflammatory and fibrogenic stimuli, quiescent ito cells do not only transform into a fibrogenic phenotype (myofibroblasts) but also proliferate and increase the synthesis and the accumulation of extracellular matrix (ECM) in liver sinusoidal space. HSC morphological transformation represents the crucial pathological event for the initiation of fibrogenesis and its progression to fibrotic liver disease. As a result, increased output of fibrogenic and inflammatory genes mainly precede secretion of fibrogenic (transforming growth factor beta 1 [TGF-β₁]), and inflammatory (tumor necrosis factor-alpha [TNF-α], interleukin 1 beta [IL-1β], IL-6) cytokines to sustain fibrogenesis. Furthermore, there is ECM accumulation, the proliferation of myofibroblasts, and recruitment and activation of other hepatic and non-hepatic cells in an autocrine and paracrine manner. If left untreated, liver fibrosis progresses to cirrhosis, but this transition can be hastened by comorbidity factors including HBV and hepatitis C viral (HCV) infections and alcohol abuse [Figure 2]. Cirrhosis is a manifestation of advanced liver fibrosis and it is characterized

by hepatic nodules that progressively distort normal hepatic architecture and function resulting in increased resistance to portal blood flow. These pathological events elevate sinusoidal pressure leading to portal hypertension and the risk of HCC

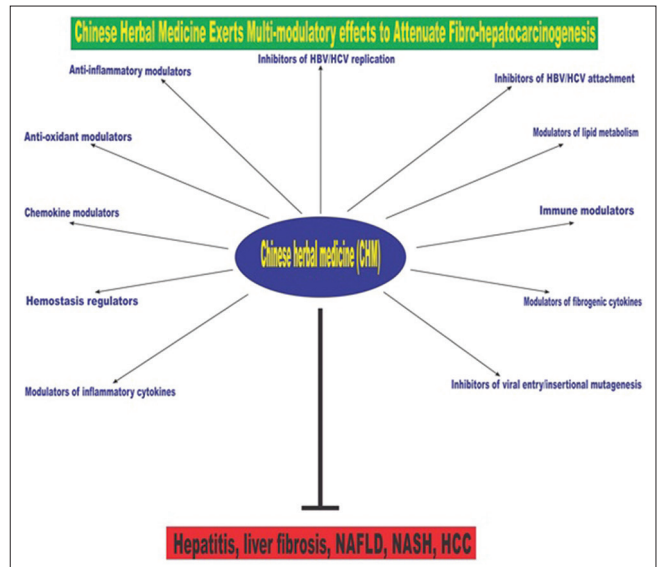


Figure 1: A diagrammatic depiction of the multi-modulatory and multi-target pharmacological effects of Chinese herbal medicine (CHM) which underpin the promising efficacy of CHM against liver disease in general

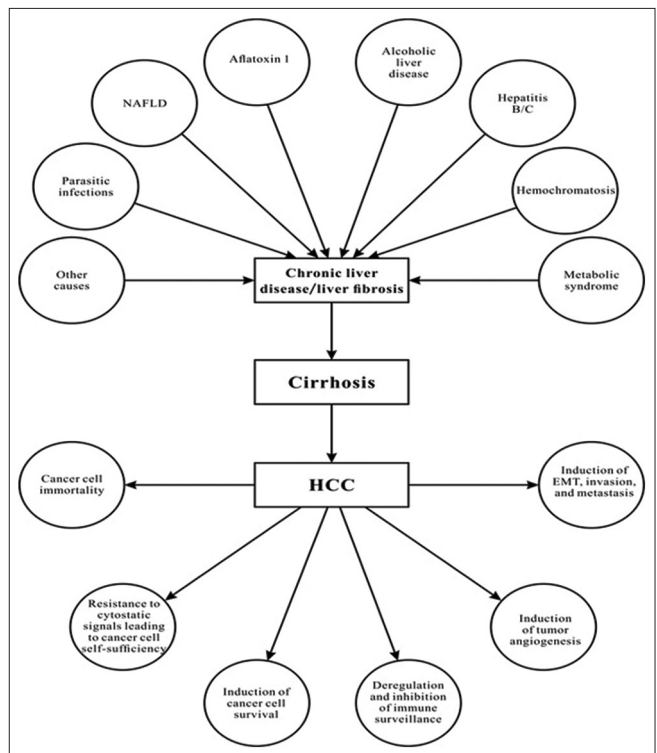


Figure 2: An illustration of the multi-etiology of fibro-hepatocarcinogenesis. Many etiological factors may act synergistically to promote progression of chronic liver injury to liver fibrosis and cirrhosis if left untreated, and this ultimately increases the risk of HCC and the manifestation of the six phenotypic hallmarks of HCC

and death [12]. Underpinning fibro-hepatocarcinogenesis is a constellation of dysregulated cell signaling pathways mainly mediated by growth factors, cytokines, chemokines, transcriptional factors, and their resultant target genes. Thus, molecular underpinnings of fibro-hepatocarcinogenesis are not only diverse but also play crucial roles in homeostasis.

The progression of liver fibrosis to cirrhosis through to HCC usually takes many years or decades. In view of this, most infected persons are asymptomatic [13]. However, this progression can be hastened within few months by factors such as neonatal liver disease, HCV infections, human immunodeficiency virus/HBV/HCV co-infections, severe delta hepatitis, and drug-induced liver disease [13]. HCC accounts for most liver-related mortality [14] and tumor progression is implicated as the main cause of death in HCC patients [15]. Furthermore, a significant percentage of patients may die from other complications arising from liver fibrosis and cirrhosis such as ascites, spontaneous peritonitis, hepatic encephalopathy, hepato-pulmonary syndrome, porto-pulmonary hypertension, and pain. The early detection and treatment of liver fibrosis and cirrhosis are crucial for overall management of HCC risk. However, the treatment of HCC is a major problem partly because of its complex nature such as high degree of cancer clonal heterogeneity, intra-tumor genetic heterogeneity, and emerging compensatory pathways in response to therapy-related inhibition of some pathways in cancer [5,16]. Among primary liver cancers, HCC represents the major histological subtype, accounting for 70-85% of the total liver cancer burden worldwide [4].

EPIDEMIOLOGY OF LIVER DISEASE IN CHINA

China has the largest population (1.3 billion people) in the world comprising 56 different ethnic groupings [17]. With the establishment of Central Cancer Registries by the Health Ministry of China in 2002 to take records of cancer cases and deaths, there has been a consistent increase in both the incidence and mortality of cancer [18-20]. For example, in 2006 the 3rd National Death Survey report showed that cancer is the second leading cause of death in China, before then a report from 2004 to 2005 had placed the national mortality rate of cancer at 135.88/100,000, with 170.17/100,000 in males and 99.97/100,000 in females (Ministry of Health, National Death Survey Report 2004-2005, Beijing). Liver cancer is the third reported cancer case in both rural and urban China and among the top 10 cancers in recent years [21]. HBV and alcohol abuse which account for the most reported cases of liver fibrosis and cirrhosis were reported to have changed, with the former decreasing while the latter increases [21]. Hospitalization due to the alcohol-related and non-viral-related cirrhosis was shown to have increased [21]. Viral related liver disease burden has increased quite significantly. For example, in Guangdong province (the most populous province in China), the predicted annual cost of HBV-related liver disease was purged at RMB 10.8 billion [22], speculatively, more than twice the annual budget of a developing country. Meanwhile, novel therapeutic agents locked up in CHMs remain untapped or poorly explored. If this rich readily available ethnobotanical heritage is properly

harnessed through cutting edge scientific approaches, it can save the increasing disease burden.

CHMS EXERT ANTI-INFLAMMATORY EFFECTS

Chronic hepatic inflammation has been widely implicated in the initiation of liver fibrosis [23-25]. Many CHMs produce their effects by modulating pro-inflammatory factors including IL-1 β , IL-2, IL-6, IL-8, IL-12, TNF- α , nuclear factor kappa B (NF- κ B), prostaglandin E₂ (PGE₂), interferon gamma (IFN- γ), nitric oxide (NO), cyclooxygenase-2 (COX-2), intercellular adhesion molecule 1 (ICAM-1), and activator protein 1 (AP-1). The modulation of inflammatory mediators and their downstream protein scaffolds have become crucial targets for the treatment of liver fibrosis, cirrhosis, and HCC. Below are some specific inflammatory mediators modulated by some CHMs to cause attenuation of fibro-hepato-carcinogenesis.

NF- κ B

NF- κ B is an important target for therapy against liver fibrosis, in view of its role in inflammation. Lu *et al.* had demonstrated that myeloid differentiation protein 88 (MyD88) inactivated phosphorylation of I κ B α in an NF- κ B/I κ B α trimmer complex leading to activation of I κ B α and toll-like receptors (TLRs) [26], and this cascade led to the release of pro-inflammatory cytokines [27]. The role of NF- κ B activation in inflammation, particularly how it induces the expression of pro-inflammatory cytokines, cell cycle regulatory molecules, and angiogenic factors have been elaborated [28]. By using a direct kinase assay and immunoblot analyses, it was shown that a seed extract of *Phaseolus angularis* markedly inhibited NF- κ B expression and effectively ameliorated hepatic inflammation [29]. An extract of *Cinnamomum cassia* inhibited mRNA expression of induced nitric oxide synthase (iNOS), COX-2, and TNF- α through suppression of NF- κ B activation [30]. Furthermore, an extract from the roots of *Polygala tenuifolia* inhibited the translocation of NF- κ B by blocking TLR4 and MyD88 expression in lipopolysaccharide (LPS)-stimulated BV2 cell lines [31] indicating that TLRs and adaptor proteins such as MyD88 could be important targets of some CHMs.

TNF- α

A number of CHMs inhibited TNF- α expression to modulate TNF- α in experimentally induced liver fibrosis. CHMs with specific negative modulatory effects on TNF- α include extracts from *Zanthoxylum schinifolium* [32], *P. tenuifolia* [31], *Clematis chinensis* [33], and *Angelica sinensis*, and *Sophora flavescens* [34].

IL

Interleukins play crucial roles in the inflammatory reactions including cell adhesion, neutrophil aggregation, inflammatory gene expression, and release of neurotoxic substances to exacerbate inflammatory response. Inhibition of interleukins by CHMs may significantly account for the anti-inflammatory

effects of most CHMs. Extracts from *Glossogyne tenuifolia* [35], *Vitex trifolia* [36], *Glycyrrhiza uralensis* [37], *Scutellaria baicalensis* and *Andrographis paniculata* [38], *Caesalpinia sappan* [39,40], and *Phellodendron chinense* [41] were shown to have down-regulated expression of IL-1 β , IL-2, IL-6, and IL-12. IL-10 has severally been reported as a negative regulator of inflammation [42]. The mechanism of IL-10-dependent anti-inflammatory effect is linked to suppression of inflammatory cytokines [43]. Some CHMs were reported to have up-regulated IL-10 expression. Example, the root extracts of *Astragalus membranaceus* reversed down-regulation of IL-10 expression under colitis-inducing conditions [44].

IFN- γ

The role of IFN- γ in inflammation has been well-elaborated [45]. IFN- γ activates macrophages to release IL-1, TNF- α , IL-6, IL-8 and several other pro-inflammatory mediators, playing major roles in inflammation. A root extract of *A. membranaceus* markedly reduced the expression of IFN- γ [44].

PGE₂

PGE₂ causes vasodilation of peripheral blood capillaries at inflammatory site, thereby increasing vascular permeability, plasma exudation, edema, and inflammation and these effects can potentiate inflammatory reaction. Therefore, cessation of PGE₂ activity may enhance anti-inflammation. An extract of *Houttuynia cordata* successfully inhibited PGE₂ release in LPS-induced activation of mouse peritoneal macrophages [46]. Similarly, extracts of the flowers of *Carthamus tinctorius* markedly reduced the release of PGE₂ [47].

iNOS and NO Production

Vascular dilatation, vascular permeability, cell infiltration, and release of pain mediators are all orchestrated by NO production under the regulation of iNOS in smooth muscle cells. Inhibition of this pathway may significantly halt inflammation and its associated complications. Lim *et al.* had reported inhibition of iNOS-dependent NO synthesis from RAW 264.7 cells by the action of phylligenin, a compound isolated from *Forsythia koreana* and it led to abrogation of the inflammatory response in the studied cells [48].

COX-2

COX-2 is a member of the cyclooxygenase family. It is constitutively expressed on inflammatory cells [49]. It is only expressed on tissues secondary to stimulation by inflammatory stimuli or tissue injury. A number of CHMs have been shown to markedly decrease iNOS and COX-2 expressions in experimental models of liver fibrosis. For example, extracts of the Ramulus of *Taxillus liquidambaricola* [50], and the aerial parts of *Pogostemon cablin* [51]. Further, some CHMs were shown to down-regulate a panel of pro-inflammatory mediators including IL-1 β , TNF- α , iNOS, ICAM-1, and COX-2. A typical example is the extracts of *A. sinensis* and *S. flavescens* which significantly inhibited

IL-1 β , TNF- α , iNOS, ICAM-1, and COX-2 [34]. Extracts of *P. angularis* inhibited NF- κ B and AP-1 [3].

Mitogen-activated Protein Kinases (MAPKs)

MAPK pathway is crucial in inflammatory responses, particularly its downstream mediators such as p38. Essentially, p38 enhances assembly and activation of leukocytes, regulates transcription factors and cytokine biosynthesis [3]. MCP-1 regulates many cells in the inflammatory process such as mononuclear cells, B cells, and T cells causing cell migration and aggregation at the site of inflammation. p38 and MCP-1 represent major targets for anti-inflammatory agents. Many CHMs exert their effects by inhibiting p38, and MCP-1 mRNA expression. For instance, extract of *Z. schinifolium* suppressed p38 and TNF- α -induced MCP-1 expression [32]. It was practically impossible to include in this review all CHMs with anti-inflammatory effects, and we seldom tried it, nonetheless those captured in this review comprehensively reflect the general picture. We wish to state that there are many other CHMs with anti-inflammatory effects, which readers can source elsewhere.

CHMS DEMONSTRATE INHIBITION OF HSC ROLE IN FIBROGENESIS

Many reports have conclusively implicated HSCs as the main hepatic cell responsible for liver fibrosis [52,53]. CHMs may interrupt one or more stages of HSC transformation, to attenuate liver fibrosis. For example, genipin, an isolate from one of the herbal components of *Yinchenhao Tang*, suppressed wound-induced HSC migration and proliferation to ameliorate liver fibrosis [54].

HSC Activation

HSC activation was also inhibited by Fuzheng Huayu, Chinese herbal formula, through blockade of fibronectin/integrin-5 β 1 signaling pathway [55,56]. Xiao Chaihu Tang inhibited HSC proliferation by suppressing cell secretion [57]. Root extracts of two Chinese herbs (*A. membranaceus* and *Salvia miltiorrhizae*) inhibited HSC activation and proliferation in keloid fibroblasts [58].

HSC Proliferation

Gypenosides inhibited platelet-derived growth factor (PDGF)-induced HSC proliferation via suppression of PDGF-Akt-p70^{S6k} and inhibition of cyclin D1 and D2 expression [59]. Ganoderic and ganoderic acids derived from *Ganoderma lucidum* ("Lingzhi") significantly inhibited HSC proliferation via suppression of platelet-derived growth factor β receptor (PDGF β R) phosphorylation [60].

HSC Apoptosis

Some CHMs selectively inhibited hepatocyte apoptosis but enhanced apoptosis of HSCs. Genipin, the pharmacologically active agent isolated from one of the herbal components

of Yinchenhao Tang inhibited *in vitro* TGF- β_1 -induced hepatocyte apoptosis [61]. Subsequently, it was confirmed that genipin suppressed hepatocyte apoptosis in primary cultured murine hepatocytes via Fas-mediation [62]. Further genipin-treated mice resisted Ca²⁺-induced mitochondrial permeability transition (MPT) compared to control and model [63]. Tetrandrine, an isolate from the roots of *Stephania tetrandrae* potentially induced apoptosis of T-HSC/Cl-6 cells by activating caspase-3 protease and cleavage of poly (ADP-ribose) polymerase [64].

CHMS EXERT ANTI-OXIDANT AND ANTI-LIPID PEROXIDATIVE EFFECTS

Many CHMs inhibit oxidant and lipid peroxidation while at the same time enhance in-built hepatic antioxidant machinery to attenuate reactive oxygen species (ROS)-mediated inflammation and fibrogenesis. The production of ROS in hepatocytes as well as perisinusoidal cells has been attributed to many factors including oxidant activity, lipid peroxidation, mitochondrion electron transport chain, damaged mitochondria, cytochrome P450 isoforms, e.g., P450 2E1 (CYP2E1), xanthine oxidases, nicotinamide adenine dinucleotide phosphate oxidases, and altered metabolism [65]. ROS-dependent oxidative stress causes increase in MPT leading to hepatocyte necrosis and apoptosis [24]. Moreover, ROS (e.g. hydrogen peroxide, superoxide radical, and nitrosative species) increases the expression of specific genes linked to fibrogenesis, among which are pro-collagen type 1, monocyte chemoattractant protein 1 (MCP-1), and tissue inhibitor of metalloproteinase-1 (TIMP-1) through activation of many signal transduction pathways and transcription factors such as c-jun N-terminal kinases, AP-1, and NF- κ B [66]. ROS generated by activated Kupffer cells and damaged hepatocytes activate HSCs by increasing their fibrogenic potential. It is therefore of enormous significance in the treatment of liver disease to arrest or suppress oxidative stress and lipid peroxidation. A typical CHM shown to produce suppression of oxidant and lipid peroxidation activities is extracts from *S. miltiorrhizae*. Extracts from *S. miltiorrhizae* enhanced superoxide dismutase (SOD) activity while reducing malondialdehyde (MDA) levels in experimentally induced liver fibrosis [67]. Furthermore, extracts from *S. miltiorrhizae* up-regulated glutathione levels whilst at the same time reduced lipid peroxidation in a dose-dependent manner [68]. Other CHMs have shown significant anti-oxidant and anti-lipid peroxidation effects both *in vitro* and *in vivo* by reducing oxidant biomarkers (MDA, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase), fibrogenic biomarkers (hyaluronic acid, laminin, type III procollagen, and type IV collagen) but increased anti-oxidant activity (increased glutathione S-transferase and SOD activities). CHMs in this group (anti-oxidant and anti-lipid peroxidation promoters) worth mentioning include *Panax notoginseng* (Tianqi) extract [69], *Ginkgo biloba* (Yinxing) extract [70], berberine [71,72], Yinchenhao Tang extract [72], extract of *Solanum nigrum* [73], Xiao Chaihu Tang [74], Handan Ganle, taurine [75], and

several other CHMs [Table 1].

CHMS EXERT ANTI-VIRAL REPLICATIVE EFFECTS

Cessation and inhibition of virus-derived ROS are important in the treatment of hepatitis-related liver fibrosis. Worldwide HBV and HCV have been acclaimed as the most common causes of chronic liver disease [4]. Pathologically, HBV can integrate into host genome (insertional mutagenesis) to induce chromosomal instability leading to liver disease progression. Unlike HBV, various HCV proteins such as core protein, the envelope, and non-structural proteins have been shown to exert oncogenic potential [24]. Several CHMs were shown to exert antiviral effects in both pre-clinical and clinical studies. *In vitro* berberine, artemisinin and artesunate inhibited viral reproduction [143]. Other CHMs including aucubin [144], nobiletin an isolate from the peelings of *Citrus unshiu* [145], and oxymatrine [146] inhibited viral reproduction and replication. *Handan Ganle* inhibited viral replication in patients with decompensated cirrhosis [147]. Moreover, *Xiao Chai Hu Tang* enhanced IFN- γ and antibody production against hepatitis B core and antigens in chronic HBV patients [148].

CHMS PRODUCE IMMUNOMODULATORY EFFECTS

TGF- β and PDGF are the two most potent fibrogenic cytokines [24] and have classically been considered to provide fibrogenic and proliferative stimuli to HSC.

TGF- β

The specific role of TGF- β in liver fibrosis has severally been elucidated [149,150]. Yang *et al.* have shown effective modulation of TGF- β /Smad signaling by a synergized root extract derived from *A. membranaceus* and *S. miltiorrhiza*, which led to decreased fibrogenic biomarkers and liver fibrosis [9]. Subsequently, the synergized root extract inhibited TGF- β_1 -induced HepG2 cell proliferation and invasion by modulating TGF- β /Smad signaling [151]. The synergized root extract suppressed DEN-induced HCC, decreased pro-neoplastic markers (GGT and GST-P) and down-regulated PAI-1 mRNA expression in TGF- β_1 -stimulated HepG2 cells [152]. To further elaborate the mechanism of action of the synergized root extract, it was observed that it switched pSmad3L-dependent signaling (oncogenic) to that of pSmad3C (tumor suppression) [153]. *S. miltiorrhiza* extracts A&B down-regulated TGF- β_1 , and TIMP-1 gene expressions and blocked MAPK activity [154]. Rehin and emodin, isolated from *Rheum palmatum* inhibited TGF- β_1 expression [155]. *Buzhong Yiqi Tang* and *Renshen Yangrong Tang* produced significant immunomodulatory effects to reduce liver fibrosis [156]. Put together, this observation with specific regard to the synergized root extract needs further investigations, in view of the fact that DEN-induced HCC model is highly sensitive and accurately mimic the pathological features of human liver fibrosis and HCC [157]. Many other Chinese herbal formulae modulate several signaling pathways at multi-level to produce anti-fibro-

Table 1: A list of some extracts and isolated phyto-compounds from CHMs and their mechanisms of action against fibro-hepato-carcinogenesis

Phyto-compound	Botanical source	Pharmacological activity	Putative mechanism of action	Target	References
Phenyl ethanol glycosides (glycosides)	<i>Cistanche tubulosa</i>	Anti-fibrotic, hepatoprotective	Restores ECM metabolism by modulating TGF- β_1 -dependent signaling	TGF- β , NF-kB	[76]
Berberine (quaternary ammonium salt)	<i>Coptis chinensis</i>	Anti-lipogenic, hepatoprotective	Represses expression of lipogenic genes; general restoration of hepatic lipid metabolism	IRS-1, SREBP1c, CPT1, SCD1, FAS	[77-80]
Ombuine (flavonoid)	<i>Gynostemma pentaphyllum</i>	Anti-lipogenic, hepatoprotective	Repression of lipogenic genes to restore hepatic lipid metabolism	NO, AST, ALP, TMAO, insulin pathway	[81-83]
Glycyrrhizin ^b	<i>Glycyrrhiza uralensis</i>	Anti-hepatocarcinogenic	Inhibits HBV replication; modulates PLA2; activates IL-10 activity	PLA2, IL-10	[84-89]
Silymarin ^a (silibinin, isosilibinin, silicristin, silidianin) (flavonolignans)	<i>Silybum marianum</i>	Anti-viral	Blocks integration of virus DNA into host cells; inhibits absorption and translocation of transferrin	Apolipoprotein B, IL-10, AST	[90-94]
Quercetin rhamnoside, gallic acid, geraniin, quercetin glycoside	<i>Phyllanthus niruri</i>	Anti-viral, anti-hepatotoxic	Clears viral proteins (HBsAg, HBeAg, HBV DNA)	Annexin A7 protein	[95-97]
Resveratrol, polydatin (anthraquinones)	<i>Polygonum cuspidatum</i>	Anti-viral, hepatoprotective	Represses expression of HBeAg, HBV DNA	HBeAg, HBV DNA	[98-100]
Saikosaponins C ^b and B2 (terpenoids)	<i>Bupleurum chinense</i>	Anti-oxidant, hepatoprotective, anti-viral	Free radical scavenging of reactive chemical species; suppresses viral attachment, entry and fusion	Viral homing factors	[101-106]
Astragaloside ^a , astragalus polysaccharide, salvianolic acid (flavonoids and saponins)	<i>Salvia miltiorrhiza</i> , <i>Astragalus membranaceus</i>	Anti-viral, anti-fibrosis, anti-HCC	Attenuate fibrosis and HCC by modulating fibrogenic factors	MAPKs, TGF- β , Smad proteins, Imp7/8, PAI-1, GSH, SOD, MMP9, NF-KB, TNF- α	[107-112]
Matrine, oxymatrine (alkaloids)	<i>Sophora flavescens</i>	Anti-viral, anti-inflammatory	Improves liver vasomotion in NO-dependent manner	TLR9, IL-8, IL-6, sICAM-1, eNOS	[113-115]
Periplocoside A (pregnane glycosides)	<i>Periploca sepium</i>	Hepatoprotective	Reverses liver damage by modulating inflammatory cytokines and hepatic enzymes	IL-4, IFN- γ	[116,117]
Baicalin ^b	<i>Scutellaria baicalensis</i>	Anti-inflammatory, anti-oxidant, hepatoprotective	Attenuates liver injury via chelation and anti-oxidant activity	SOD, GSH, NF-kB, JNK, ERK, IL-6, TNF- α	[118-122]
Lignans, schischinone, schisandrin B (lignans)	<i>Schisandra chinensis</i>	Anti-viral, anti-inflammatory	Inhibits viral replication; increases HO-1 expression	HO-1, NF-kB, Nrf2	[123,124]
Extracts of Panax	<i>Panax notoginseng</i>	Anti-oxidant, hepatoprotective, anti-inflammatory	Attenuates NAFLD in rats by modulation both inflammation and lipid accumulation	MDA, GSH, CYP2E1, SOD, TNF- α , IL-6	[125-127]
Penta-oligogalacturonides (glucuronides)	<i>Crataegus pinnatifida</i>	Anti-oxidant, anti-lipidemic	Negatively regulate triglycerides, PAP, and GPAT	Acyl-CoA oxidase, 3-ketoacyl-CoA thiolase, carnithine palmitoyltransferase I, PAP	[128,129]
Kernels of Prunus	<i>Prunus armeniaca</i>	Anti-steatosis, anti-oxidant, free radical scavenging activity	Attenuates experimental liver steatosis via regulation of lipid metabolism and hepatic enzymes	ALT, AST	[130,131]
Saucerneol G (lignans)	<i>Saururus chinensis</i>	Anti-fibrotic, hepatoprotective, anti-inflammatory	Attenuates liver fibrosis in rats by regulating hepatic enzyme and anti-oxidant activity	MDA, ALT, AST, HA, SOD, NF-kB, MAPKs	[132,133]
Salvianolic acid ^a B	<i>Salvia miltiorrhiza</i>	Anti-fibrotic, hepatoprotective	Inhibits HSC activation, ECM accumulation and HSC proliferation by modulating TGF- β_1	TGF- β_1 , TIMP1	[134,135]
Extract of Brucea	<i>Brucea javanica</i>	Anti-cancer, pro-HCC-specific apoptosis	Selectively induces HCC apoptosis by activating mitochondria-dependent apoptotic pathways	Cytochrome c, caspase3	[136,137]

(Contd...)

Table 1: (Continued)

Phyto-compound	Botanical source	Pharmacological activity	Putative mechanism of action	Target	References
Dioscin (steroidal saponins)	<i>Dioscorea opposita</i>	Anti-oxidant, anti-inflammatory, hepatoprotective	Attenuates NAFLD by modulating lipogenic and fibrogenic signaling	MAPK pathway, AST, ALT, NF-κB, TLR4, MyD88	[84,138,139]
Gallic acid (trihydroxybenzoic acid)	<i>Punica granatum</i>	Anti-oxidant, hepatoprotective	Attenuates NAFLD in rats by modulating choline metabolism and enhanced anti-oxidant activity	TAG, choline	[140,141]
Camptothecin (alkaloidal quinoline)	<i>Camptotheca acuminata</i>	Anti-HCC	Promotes HCC-specific apoptosis via TRAIL-mediated	TRAIL, ERK, p38	[142]

ECM: Extracellular matrix, TGF-β: Transforming growth factor beta, NF-κB: Nuclear factor kappa B, FAS: Fatty acid synthase, SCD1: Stearoyl-CoA Desaturase1, IRS1: Insulin receptor substrate, CPT1: Carnitine palmitoyltransferase 1, SREBP: Sterol regulatory element-binding protein, CHM: Chinese herbal medicine, NO: Nitric oxide, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, TAMO: Trimethylamine N-oxide, PLA2: Phospholipase A2, HBV: Hepatitis B virus, IL: Interleukin, HBsAg: Hepatitis B surface antigen, HBeAg: Hepatitis B e antigen, HCC: Hepatocellular carcinoma, MAPKs: Mitogen-activated protein kinases, GSH: Glutathione, SOD: Superoxide dismutase, TNF-α: Tumor necrosis factor-alpha, PAI-1: Plasminogen activator inhibitor-1, MMP9: Matrix metalloproteinase 9, TLR: Toll-like receptors, ICAM-1: Intercellular adhesion molecule 1, eNOS: Endothelial NOS, IFN-β: Interferon gamma, JNKs: c-jun N-terminal kinases, MDA: Malondialdehyde, ALT: Alanine aminotransferase, HA: Hyaluronic acid, TIMP1: Tissue inhibitor of metalloproteinase-1, NAFLD: Nonalcoholic fatty liver disease, PAP: Phosphatidic acid phosphohydrolase, MyD88: Myeloid differentiation protein 88. ^a: (Have shown efficacy against hepatitis, liver fibrosis, fatty liver disease, cirrhosis and HCC); ^b: (Have shown efficacy against hepatitis, fatty liver disease, and cirrhosis); names in parenthesis '()' represent chemical classes

Table 2: Some CHM formulas, their composition and putative mechanisms of action against fibro-hepato-carcinogenesis

Name of Chinese herbal formula	Constituent herbs	Traditional Chinese indication	Current indication	Mechanism of action	References
Biejia* Ruangan tablets	<i>Placenta hominis</i> , <i>Radix notoginseng</i> , <i>Radix codonopsis</i> , <i>Astragalus membranaceus</i> , <i>Radix isatidis</i> , <i>Fructus forsythia</i> , <i>Rhizoma curcumae</i> , <i>Radix Paeoniae rubra</i> , <i>Radix angelica sinensis</i>	Enhances portal circulation and dissolves hepatic lumps	Anti-fibrotic, hepatoprotective	It produces hepatoprotection by regulating ECM metabolism mainly downregulating the expression of matrix proteins. TIMP-1 suppression in TGF-β/Smad3-dependent manner	[158,159]
Huanglian* Jiedu decoction	<i>Fructus gardeniae</i> , <i>Cortex phellodendri</i> , <i>Rhizoma coptidis</i> , <i>Scutellariae baicalensis</i>	Dissipates heat from qi	Anti-HCC, anti-cancer	Inhibits tumor growth, proliferation, angiogenesis via suppression of eEF2	[160]
Fuzheng* Huayu tablet	<i>Gynostemma pentaphyllum</i> , <i>Salvia miltiorrhiza</i> , <i>Semen persicae</i> , <i>Fructus Schisandrae chinensis</i> , <i>Pollen pini</i> , <i>Radix fermentation mycelium</i>	To enhance blood flow, blood thinner, invigorates the liver	Treatment of HBV/HCV-related liver fibrosis	Its anti-fibrotic activity is attributed to repression of oxidant genes and modulation of TGF-β/Smad, VEGF and BM-7 signaling	[1,161,162]
Xiao Chai Hu Tang	<i>Scutellaria baicalensis</i> , <i>Bupleurum chinensis</i> , <i>Ginseng</i> , <i>Jujube</i> , <i>Licorice</i> , <i>Ginger</i> , <i>Pinellia</i>	To treat shaoyang diseases	To improve liver function; anti-HCC, anti-viral	Decreases fibrotic and oncogenic factors and genes by regulating TIMP-1, TNF-α, TGF-β/Smad signaling pathways	[57,163]
Huangqi decoction	<i>Astragalus membranaceus</i> , <i>Rhizoma glycyrrhizae</i>	Used to improve liver function	Anti-fibrotic, anti-cirrhosis	Attenuates experimental liver fibrosis via modulation of TGF-β and PDGF signaling pathways	[164]

*Contain other non-herbal components including fungi and minerals. HCC: Hepatocellular carcinoma, CHM: Chinese herbal medicine, HBV: Hepatitis B virus, ECM: Extracellular matrix, TIMP-1: Tissue inhibitor of metalloproteinase-1, TGF-β: Transforming growth factor beta, VEGF: Vascular endothelial growth factor, TNF-α: Tumor necrosis factor-alpha, PDGF: Platelet-derived growth factor

carcinogenic effects [Table 2].

PDGF

Many other CHMs in like manner have modulated cytokines involved in fibrogenesis. Example, *Ganoderma lucidum* extract and *Ganoderma* polysaccharide inhibited HSC proliferation through blockade of PDGFβR phosphorylation [165]. *Berberis anistata* fruit extract down-regulated expression of NF-κB,

α-SMA, and TGF-β₁ [166,167]. *Ginkgo biloba* extract down-regulated expression of NF-κB, TGF-β₁, and collagen genes [70]. Cordyceps polysaccharide inhibited PDGF expression [168].

CHM TARGETS SPECIFIC GENES

Some CHMs exert specific effects on some genes, especially genes implicated in fibro-hepato-carcinogenesis.

c-fos and c-jun

Tetrandrine down-regulated c-fos and c-jun gene expressions, while they up-regulated expression of Smad7 [169].

Smurf2

Glycyrrhizin an isolate from *G. uralensis* decreased NF- κ B binding activity and also down-regulated smurf2 gene expression [63]. *Buzhong Yiqi Tang* and *Renshen Yangrong Tang* produced significant immunomodulatory effects to reduce liver fibrosis [156].

CONCLUSION

Admittedly, pathogenesis of liver disease is complex, normally enjoying the participation of many cell types, cytokines, chemokines, adhesion molecules and genes, notwithstanding, efforts should be made to tailor scientific investigations to specific targets which are crucial for treatment of liver diseases. It is heartwarming the array of isolated phyto-compounds from CHMs which have demonstrated efficacy against various pathological manifestations of fibro-hepatocarcinogenesis such as liver fibrosis, steatohepatitis, cirrhosis, and HCC. Indeed, there has been an increased effort to characterize these phyto-compounds in the light of their reported indigenous uses but more still needed to be done. For instance, efforts should be focused on structure activity relations of these compounds to help advance understanding on their specific effects at the molecular level. It is long held that Chinese herbal formulas are the historical antecedents of modern-day combination therapy, valid as it may be, it is important that future studies thoroughly investigate individual compounds as single chemical entities, then their combined effects can be predicted with certainty. As it is now, it is difficult to tell which compound or extract from which component herb is producing which effect and to what extent. Although the “one fits all” leaning of westernized medicine is without challenges, it is also important that “many fits all” characteristic of CHMs is subjected to thorough component analysis. We agree with others who are in support of combinatorial approach since it taps into the enhanced synergistic actions of many compounds with varying pharmacological activities. However, the question of herb-herb and herb-drug interactions remains outstanding just as toxicity details. It is worth notice that future studies should address these concerns. CHMs exert multi-modulatory and multi-target effects against pathological manifestations (liver fibrosis, cirrhosis, and HCC) of fibro-hepatocarcinogenesis but future research efforts must focus on structural and functional elucidation of single compounds isolated from herbal components of Chinese herbal formulae.

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