Review Article

Herbal Medicines for Hepatitis C Virus Infection: The Exploratory Journey from Bench to Bedside Still Has a Long Way to Go

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Abstract

Hepatitis C virus (HCV) infects at least 150 million people chronically worldwide. It is a major risk factor for cirrhosis, hepatocellular carcinoma, and death. Direct-acting antiviral therapy is very efficacious in treating HCV infection but it is inaccessible and unavailable in some developing countries. Therefore, searching for more effective and easily accessible regimens remains an urgent need. The aim of this article is to review the anti-HCV effects of herbal medicines from experimental to clinical evidence, and discuss current issues, hurdles and future perspectives for their application from bench to bedside. Numerous *in vitro* studies have indicated that many herbs work effectively in exerting anti-HCV activities. Yet, only a few animal experiments have been conducted that demonstrate the anti-HCV effects of these medicines; in addition, these results do not show an ability to eliminate the virus completely from the infected animals. Thus far, clinical trials have produced inconclusive anti-HCV results in terms of efficacy and safety, presumably due to the lack of the quality of methodologies used in the trials. In conclusion, despite apparent anti-HCV activities *in vitro*, clinical efficacy and safety of herbal medicines for the treatment of HCV infection have not been revealed convincingly. More animal studies using ideal models and more well-designed clinical trials with a larger sample sizes and longer treatment periods, taking the body habitus into consideration, are required to further assess the efficacy and safety of herbal medicines for HCV infection.

Introduction

Hepatitis C virus (HCV) is an enveloped and positive strand RNA virus of the Hepacivirus genus within the Flaviviridae family.[1] HCV chronically infects at least 150 million people worldwide, especially in central Asia and the Mediterranean, having prevalence of >3.5%).[2,3] More than 60% of acutely infected patients suffer from chronic HCV infection, which develops into cirrhosis in 5–25% of the infected patients within 25–30 years. Moreover, approximately 30% of cirrhotic patients develop decompensated liver disease within 10 years, and 1–3% of them develop hepatocellular carcinoma eventually.[1,4] Thus, HCV infection is one of the major global health problems.

Herbal medicines, which have been used to treat various diseases for thousands of years, especially in traditional Chinese medicine, have become a main component of complementary medicine in the West.[5] Various herbal medicines, including formula, extracts and compounds derived from herbs, have been used for treatment of liver diseases, including chronic hepatitis B, chronic hepatitis C (CHC), alcoholic liver disease, and nonalcoholic fatty liver disease.[6–11] Over the past few decades, particular attention has been paid to the potential anti-HCV effects of herbal medicines, and most of *in vitro* (in hepatic cell lines) and *in vivo* (in animals) studies have shown significant anti-HCV effects for a number of herbal medicines.

To evaluate the clinical efficacy and safety of herbal medicines in patients with CHC, many clinical studies, including randomized controlled trials (RCTs), have been carried out. Although herbal medicines perform well in reducing risk of liver cirrhosis and overall mortality in the patients with HCV,[12] their clinical efficacy, in

Keywords: Herbal medicine; Hepatitis C virus; Efficacy; Safety.

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; CHC, chronic hepatitis C; DAA, direct-acting antiviral agent; ETVR, end-of-treatment viral response; GGT, γ-glutamyl transferase; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; HCV, hepatitis C virus; Peg-IFN, pegylated-interferon alpha-2a; RCT, randomized controlled trials; SVR, sustained virological response; XCHT, Xiao-Chai-Hu-Tang.

Received: May 26, 2019; Revised: June 18, 2019; Accepted: June 24, 2019

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How to cite this article: Yang X-Y, Zhang Y-Y, Xie W-R, He SH, Wu L-H, He X-X, Xia HH-X. Herbal Medicines for Hepatitis C Virus Infection: The Exploratory Journey from Bench to Bedside Still Has a Long Way to Go. *J Explor Res Pharmacol* 2019;4(2):9–18. doi: 10.14218/JERP.2019.00003.

terms of clearance of serum HCV RNA, remains inconclusive. In this article, we review the anti-HCV effects of herbal medicines from experimental to clinical evidence, and discuss the current issues and hurdles, and future perspectives for their application from bench to bedside.

Current treatment for HCV infection

HCV life cycle includes the entry of HCV particle into hepatocytes, translation and replication of HCV RNA, and assembly, budding and secretion of HCV.[13,14] The HCV genome is approximately 9.6 kb of uncapped RNA.[15] The HCV RNA encodes a polyprotein, which is processed by host and viral proteases into at least 10 products. These products include structural proteins, such as Core, E1 and E2, and nonstructural proteins, such as NS2, NS3, NS4A, NS4B, NS5A and NS5B.[15] All the nonstructural polypeptides are potential targets for drug therapy.

Treatment of HCV infection is experiencing rapid progress. Before the advent of the direct-acting antiviral agent (DAA), including inhibitors of polymerase, NS5A and protease, pegylated interferon (peg-IFN) and ribavirin were considered as the standard-of-care treatment, yielding sustained virological response (SVR) rates of approximately 50% for genotype 1 patients.[16,17] The first-generation protease inhibitors boceprevir and telaprevir were approved in 2011. Triple regimens with boceprevir or telaprevir, plus peg-IFN and ribavirin initiated the era of DAA therapy,[18,19] with SVR rates of 67–75% for naïve patients. However, the development of resistance-associated virus variants and severe adverse events (AEs) restricted this triple therapy regimen.

For the polymerase inhibitors (*e.g.*, sofosbuvir and dasabuvir), the new-generation drugs (*e.g.* simeprevir and grazoprevir) and NS5A inhibitors (*e.g.* ledipasvir and velpatasvir) were approved soon after. IFN-free combination regimens, consisting of one to two DAAs from different classes based on the HCV genotype with or without ribavirin, had been recommended as the first-line standard-of-care treatment for CHC in European countries up to 2017.[20] Due to the virological efficacy (high SVR rates, up to 90%), safety and tolerability, the European Association for the Study of the Liver recommended in 2018 an IFN-free, ribavirin-fee, DAA-based regimens as the preferred options for treating HCV-infected patients without cirrhosis or with compensated cirrhosis.[21] Therefore, DAA therapy has been verified to be very efficacious for HCV infection; however, in many developing regions of the world, HCV remains uncontrolled due to inaccessibility and unavailability of DAA-based regimens.[3,22] Therefore, searching for more effective and easily accessible regimens remains an urgent need.

Experimental evidence of herbal medicines against HCV

In vitro **studies**

A number of *in vitro* studies have been carried out to identify the herbal medicines with effective anti-HCV activity. A multitude of herbal medicines, including extracts and formulas, have demonstrated anti-HCV effects. The effects and mechanisms by which these herbal medicines inhibit HCV infection are listed in Table 1.[23–51] According to the modes of action, we have classified, here, these anti-HCV herbal medicines into three forms: (1) NS protein inhibition; (2) HCV entry inhibition; and (3) others, as described below.

NS protein inhibition

Methanolic extracts of *Acacia nilotica*, *Boswellia carterii*, *Embelia schimperi*, *Quercus infectoria*, *Trachyspermum ammi*,[23] *Phyllanthus amarus* and *Terminalia arjuna*,[24] water extracts of *Piper cubeba, Q. infectoria, Syzygium aromaticum* and *Embeliaribes,*[23,25] ethanol extracts of *Rhodiola kirilowii* (Regel) Maxim,[26] *Saxifraga melanocentra* and *Spatholobus suberectus*,[27,28] and other extracts of *Galla Chinese*,[29] *Magnolia officinalis* (*Hou-Pu*) and *Solanum nigrum* seeds all have shown inhibitory effects on the NS3 protease,[30,31] while ethanol extract of *V. Vinifera* root has shown inhibitory effect on the NS3 helicase. All of those extracts demonstrated potent reduction of HCV RNA concentration. Besides NS3, NS5B is another dominating target. Extracts of *Phyllanthus amarus* and *Terminalia arjuna*,[24] *Fructus Ligustri Lucidi* and *Aeginetiaindica* have been shown to exert their anti-HCV effects through inhibition of the NS5B polymerase.[32,33] In addition, the NS3/4A protease, NS4A and NS5A protein have been verified as the anti-HCV targets of *Azadirachta indica* leaves,[34] *Piper cubeba, Q. infectoria, Syzygium aromaticum*,[23] *Magnolia officinalis* (*Hou-Pu*),[30] *Spatholobus suberectus* and seeds of *Silybum marianum*,[28,35] respectively.

HCV entry inhibition

As the multistep process of HCV entry into host cells, HCV entry becomes an important target of anti-HCV activities (*i.e.* its impediment). Examples of herbal medicines targeting for inhibition of HCV entry include methanolic extracts of *Bupleurum kaoi* root,[36] *Morinda citrifolia* and *Rhizoma coptidis*,[37,38] ethanol extracts of fruits of *Schisandra sphenanthera Rehd. et Wils*,[39] water extracts of wild Egyptian artichoke,[52] and other extracts of *Dipsacus asperoides*,[40] *Magnolia officinalis* (*Hou-Pu*),[30] and compounds of epigallocatechin-3-gallate, delphinidin,[41] flavone and flavan-based compounds (amentoflavone, 7,40-dihydroxyflavanone, and orobol).[42]

Others

NS protein inhibition and HCV entry inhibition are the two main anti-HCV modes of herbal medicines. Beyond those, *Nigella sativa* seed,[43] *Cinnamomi cortex*,[44] and flavone and flavan-based compounds (amentoflavone, 7,40-dihydroxyflavanone, and orobol) have been shown to exert their anti-HCV actions by inhibiting HCV replication.[42] In addition to inhibiting HCV entry at the post-binding stage, Qian *et al.*[39] found that schizandronic acid from ethanol extracts of fruits of *Schisandra sphenanthera Rehd. et Wils* impeded HCV infection by other mechanisms, including inhibition of internalization of the viral particles and blockage of intercellular spread to neighboring cells. The 7-O-methylated analogues of flavonolignans from *Silybum marianum* have been reported to prevent HCV infection by inhibiting drug metabolizing enzymes (CYP2C9, CYP3A4/5, and UDP-glucuronosyltransferases),[45] while another bioactive compound from seeds of *Silybum marianum*, silymarin (MK-001) has been shown to inhibit HCV by enhancing the Jak-STAT signaling pathway.[35]

Animal experiments

Although a number of *in vitro* studies have been conducted for

Table 1. Anti-HCV activities of herbal medicines as detected in *in vitro* studies

Herbal medicines			Bioactive compounds	Modes of action			Study
Forms		Names		NS protein inhibition	Inhibition of HCV entry	Others	
	Methanol	*Acacia nilotica, Boswellia carterii, Embelia schimperi, Quercus infectoria, Trachyspermum ammi*		NS3 protease, NS4A protein, NS5A/5B junction inhibition (≥90%)			Hussein *et al*., 2000[23]
Extracts		*Solanum nigrum* seeds		NS3 protease			Javed *et al*., 2011[31]
		Phyllanthus amarus		NS3 protease, NS5B polymerase inhibition			Ravikumar *et al*., 2011[24]
		Terminalia arjuna		NS3 protease, NS5B polymerase inhibition			Ravikumar *et al*., 2011[24]
		A. Euchroma, P. trifoliate, T. arvense					Ho *et al*., 2003[46]
		Bupleurum kaoi root	Saikosaponins		Inhibition of HCV entry		Lin *et al*., 2015[36]
		Morinda citrifolia	Chlorophyll catabolites, pheophorbide a and pyropheophorbide a		Inhibition of HCV entry and postentry		Ratnoglik *et al*., 2014[37]
		Rhizoma coptidis			Inhibition of HCV entry		Hung *et al*., 2018[38]
		Piper cubeba, Q. infectoria, Syzygium aromaticum		NS3 protease, NS4A protein, NS5A/5B junction inhibition (≥90%)			Hussein *et al*., 2000[23]
	Water	*Embelia ribes*	Flavonoid quercetin	NS3 protease inhibition			Bachmetov *et al*., 2012[25]
		Fructus Ligustri Lucidi	Oleanolic acid and ursolic acid	NS5B polymerase inhibition			Kong *et al*. 2013[32]
		Licorice	Glycyrrhizin			Against HCV 3a genotype	Ashfaq *et al*., 2011[47]
		Aeginetia indica		NS5B polymerase inhibition			Lin *et al*., 2018[33]
		Wild Egyptian artichoke	Grosheimol and cynaropicrin		Inhibition of HCV entry into target cells	Active against both cell-free infection and cell-cell transmission	Elsebai *et al*., 2016[48]
		Seeds of *Silybum marianum*	Silymarin (MK-001)	NS5A and HCV core protein expression inhibition		Enhancing signaling via the Jak-STAT pathway	Polyak *et al*., 2007[35]
	Chloroform	*Solanum nigrum* seeds		NS3 protease inhibition			Javed *et al*., 2011[31]
	Ethanol	*Rhodiola kirilowii* (Regel) Maxim	3,3′-Digalloylproprodelphinidin B2, 3,3′-Digalloylprocyanidin B2, (−)-Epigallocatechin-3-O-gallate, (−)-Epicatechin-3-O-gallate	NS3 protease inhibition			Zuo *et al*., 2007[26]

Table 1. Anti-HCV activities of herbal medicines as detected in *in vitro* studies - *(continued)*

Herbal medicines		Bioactive compounds	Modes of action			Study
Forms	Names		NS protein inhibition	Inhibition of HCV entry	Others	
	Fruits of *Schisandra sphenanthera Rehd. et Wils.*	Schizandronic acid		Inhibition of HCV entry	Inhibition of the step after host cell surface binding and internalization of the viral particles; blockage of intercellular spread to neighboring cells	Qian *et al.*, 2016[39]
	Spatholobus suberectus		NS3, NS5A and NS5B expression inhibition (JXT-E50)		Inhibition of translation of HCV RNA	Chen *et al.*, 2016[28]
	V. vinifera root	Vitisin B	NS3 helicase inhibition			Lee *et al.*, 2016[49]
	Inflorescences of *Scabiosa comosa* and *S. tschilliensis*	Chlorogenic acid and 3,5-DCQA				Ma *et al.*, 2016[50]
	Saxifraga melanocentra	18 polyphenols	NS3 protease inhibition			Zuo *et al.*, 2005[27]
EtOAc	*Galla Chinese*		NS3 protease inhibition			Duan *et al.*, 2004[29]
n-butanol/H_2O	*Dipsacus asperoides*	Oleanolic acid		Inhibition of HCV entry		Yu *et al.*, 2013[40]
Mix (water, ethyl acetate and dichloromethane)	*Eclipta alba*		NS5B polymerase inhibition			Manvar *et al.*, 2012[51]
		Epigallocatechin-3-gallate, delphinidin		Inhibition of HCV entry		Calland *et al.*, 2015[41]
	Azadirachta indica leaves	3-Deacetyl-3-cinnamoyl-azadirachtin	NS3/4A protease inhibition			Ashfaq *et al.*, 2016[34]
	Magnolia officinalis (Hou-Pu)	Honokiol	NS3, NS5A and NS5B expression inhibition	Inhibition of HCV entry		Lan *et al.*, 2012[30]
	Silybum marianum				Reduction of HCV core proteins; inhibition of drug-metabolizing enzymes (CYP2C9, CYP3A4/5, and UDP-glucuronosyltransferases)	Althagafy *et al.*, 2013[45]
		Flavone and flavan-based compounds (amentoflavone, 7,40-dihydroxyflavanone, and orobol)		Inhibition of HCV entry	Inhibition of HCV replication, and translation	Lee *et al.*, 2018[42]
	Nigella sativa seed	Alpha-zam			Inhibition of HCV replication	Oyero *et al.*, 2016[43]
	Cinnamomi cortex	Procyanidin B1			Inhibition of HCV replication and RNA synthesis	Li *et al.*, 2010[44]

Abbreviation: HCV, hepatitis C virus.

numerous herbal medicines, only two studies were carried out to assess their anti-HCV effects in animals.[39,53]

Qian *et al*.[34] used the transgenic ICR mice harboring human *SRB1*, *CD81*, *CLDN1* and *OCLN* genes to investigate the anti-HCV effects of schizandronic acid, which had been extracted from fruits of *Schisandra sphenanthera Rehd. et Wils*. They observed that HCV RNA levels in the serum were reduced in transgenic ICR mice treated with schizandronic acid for 2 weeks, with less positive HCV NS3 or core protein in hepatocytes, indicating the anti-HCV effects of schizandronic acid *in vivo*. However, the elimination of HCV infection in the infected mice was incomplete.[39]

Tang *et al*.[53] tested 20 Chinese herbs in nude mice to determine their anti-HCV effects. They found that *Radix Gentianae* (Long Dan Cao), *Radix Scutellariae* (Huang Qin), *Radix Sophoraetonkinensis* (Shan Dou Gen), *Fructus Gardeniae* (ZhiZi) and *Fructus Sophorae flavescentis* (Ku Shen) significantly inhibited the replication of HCV-RNA. Similar to the observation in the above study, none of them completely eliminated HCV from the infected mice.

Therefore, although both animal studies demonstrated anti-HCV effects of the herbal medicines studied, none of them were able to completely eliminate HCV from the infected animals.

Clinical evidence of herbal medicines against HCV

Herbal medicines have long been used worldwide for the treatment of CHC. Most studies have shown that herbal medicines can attenuate liver-related symptoms,[54] improve liver functions and quality of life,[55] prolong the progression from fibrosis to cirrhosis,[56,57] and reduce or prevent AEs such as anemia and psychiatric complications.[58,59] Some herbal medicines have been evaluated for their anti-HCV effects in patients with CHC in clinical trials, including nonrandomized and randomized trials.[54,60,61] Due to the overall low methodological quality of the nonrandomized trials, in this review we only describe the efficacy and safety of herbal medicines in patients with CHC that were evaluated in RCTs, in order to provide objective and reliable data.

A number of clinical studies have been carried out to compare the efficacy and safety between herbal therapy alone or in combination with IFN-therapy and antiviral therapy (with IFN or other agents), nonspecific nonantiviral therapy, or placebo for the treatment of CHC. In these studies, SVR (*i.e.* the lack of detectable HCV RNA in serum, representing loss of serum HCV RNA, by a sensitive test at 6 months after treatment cessation), end-of-treatment viral response (ETVR; *i.e.* undetectable HCV RNA at the end of treatment), relapse rate (*i.e.* the proportion of cases with undetectable HCV RNA at the end of treatment but detectable HCV RNA 24 weeks posttreatment), alanine transaminase (ALT) normalization, and/or occurrence of AEs were used as the outcome end-points.

General overview of clinical trials

Although experimental evidence has exhibited encouraging anti-HCV effects of herbal medicines, clinical trials have produced inconclusive anti-HCV results in terms of efficacy and safety, presumably due to the lack in quality of methodologies used in the trials.

Qin *et al*.[60] performed a meta-analysis of 51 RCTs carried out between 1993 and 2008. They showed that Chinese herbal medicines achieved a better virological response, including loss of serum HCV RNA, than nonspecific or placebo treatments, and appeared to have an clinical efficacy equal to IFN treatment, in terms of symptoms, liver function, and virological response. In addition, a combination of herbal medicine and IFN resulted in better liver function improvement and virological response than antiviral treatment alone. Serious (S)AEs have been rarely reported for patients who underwent herbal treatment.[60] These findings suggest that herbal medicines have effects in improving symptoms, liver function, and loss of HCV markers in HCV patients, with good safety profiles, and thus have potential for the clinical application to CHC patients. However, it should be emphasized that, as Qin *et al*. revealed, all RCTs included in this meta-analysis (published in Chinese) suffered from poor methodological quality, and thus the findings of this meta-analysis need to be confirmed in more rigorous clinical trials.

In 2011, Zhao *et al.*[61] reported a meta-analysis of RCTs that were carried out between 2001 and 2010 and which had at least 24-week treatment periods, to compare the clinical efficacy and safety of Chinese herbal therapy alone with that in combination with IFN therapy, and IFN therapy alone for the treatment of patients with CHC. They reported that, compared with IFN therapy alone, Chinese herbal therapy alone presented a lower relapse rate as well as a lower ETVR rate. However, a combination of IFN and Chinese herbal therapies yielded higher ETVR and SVR rates, a lower relapse rate, and more rapid ALT normalization, with fewer AEs than IFN therapy alone. These results suggest that although Chinese herbal therapy alone does not show significant anti-HCV effects compared to IFN therapy alone, it may play an additional or even synergistic role in the combined therapies. Obviously, this later meta-analysis provides more compelling data on the efficacy of herbal medicines, especially in combination with IFN-therapy. Again, these results should also be taken with caution due to the quality issues mentioned above. There has been no confirmatory and convincing clinical evidence so far to demonstrate any efficacy of any herbal medicines, in terms of SVR and ETVR.

Recent advances in clinical trials of four herbs

Despite the inconclusive outcomes from clinical trials, the exploratory journey searching for herbal medicines that are effective both *in vitro* and in clinical practice has never stopped. Currently, several herbal medicines with clinical potential are under investigation. Here, we summarize some recent advances in clinical trials of four herbs, with preliminary but encouraging results (Table 2[62–65,67–70,76]).

Silymarin

Silybum marianum shows impressive anti-HCV effects in the experimental studies, as described above. This natural herb has been used as a liver tonic for hundreds of years, and recently for the treatment of CHC. Disappointingly, most clinical trials failed to get the results expected according to those from the experimental studies. No clinically meaningful reduction in HCV RNA level was observed upon administration of *S. marianum* or silymarin (a substance derived from *S. marianum*) orally, from customary doses to high doses, and serum ALT and/or aspartate transaminase (AST) levels were not decreased in most of the studies.[62–67] Encouragingly, in 2013, Mariño *et al*.[68] and Bárcena *et al*.[69] conducted intravenous monotherapy with silibinin (the major compound of silymarin) in HCV-infected patients awaiting liver transplantation; the treatment led to significant and progressive HCV RNA decreases. This finding indicates that silibinin acts as the most potent compound of silymarin and intravenous administration is a better way

Table 2. Recent clinical trials of *Silybum marianum* (Silymarin), Xiao-Chai-Hu-Tang, TCM-700C, and Kuan Sin Yin for treatment of hepatitis C virus infection

Herbal medicines	Doses	Administration route	Control		Outcomes				Study
			No intervention	Placebo	HCV RNA level	Biochemical response			Adverse events	
						ALT	AST	Others		
Silybum marianum	160 mg three times a week for 4 weeks	Oral	√		No reduction	↓	↓		No report	Torres *et al.*, 2004[62]
Silybum marianum	600 or 1,200 mg for 12 weeks	Oral		√	No reduction	No reduction	/	GGT↓	No difference	Gordon *et al.*, 2006[63]
Silymarin	140, 280, 560 and 700 mg every 8 hours for 7 days	Oral		√	No reduction	No reduction	/		No report	Hawke *et al.*, 2010[64]
Silymarin	2,100 mg g/day for 24 weeks	Oral		√	No reduction	No reduction	/		/	Fried *et al.*, 2012[65]
Peg-IFN and ribavirin, plus silymarin	2 × 166 mg/day for 3 months	Oral		√	No reduction	No reduction	/		/	Pár *et al.*, 2009[67]
Silibinin	20 mg/kg/day for at least 21 days	Intravenous	√		↓	No reduction	/		No report	Barcena *et al.*, 2013[69]
Silibinin	20 mg/kg/day for a maximum of 21 days before liver transplantation and 7 days after liver transplantation	Intravenous		√	↓	/	/		Mild or not related to the study drug	Marino *et al.*, 2013[68]
Xiao-Chai-Hu-Tang	2.5 g (in the form of granulated powder) three times daily for 12 months	Oral			↓ (29%); ↑ (42%)	↓ (75%)	↓ (67%)		/	Deng *et al.*, 2011[70]
TCM-700C	An add-on drug (2 tablets three times daily) to conventional treatment (peg-IFN + ribavirin)	Oral		√	No reduction	No reduction	/		No difference	https://clinicaltrials.gov/ct2/show/study/NCT00556504
Kuan Sin Yin	100 mL daily for 6 weeks	Oral		√	↓	/	/	GOT, GPT ↓	No report	Liu *et al.*, 2016[76]

↓, decrease; ↑, increase; /, not mentioned. Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; HCV, hepatitis C virus; Peg-IFN, pegylated-interferon alpha-2a.

for preventing HCV replication. However, further research work is required to confirm the potent compounds and administration methods for the different herbs.

Xiao-Chai-Hu-Tang

Deng *et al.*[70] reported a single-arm phase II study evaluating the clinical efficacy of a traditional herbal formulation, Xiao-Chai-Hu-Tang (XCHT; Sho-Sai-Ko-To or Sho-Saiko-To in Japan and So-Shi-Ho-Tang in Korea) in the treatment of CHC in patients not suitable for IFN-based therapy. The results showed that ALT and AST were decreased in 75% and 67% of patients, respectively, and biopsy histology scores improved in 38% of patients. HCV viral load decreased in 29% but increased in 42% of patients. These findings suggest that XCHT may improve liver pathology in CHC patients, but its antiviral activity remains undetermined. Recently, a phase II single-arm, open-label trial to determine the effects of Sho-Saiko-To on hepatic injury in patients with CHC was completed. In this trial, improvement of 2 points or greater as per Knodell's histology activity index scores in paired comparisons of pre- and postliver biopsy is defined as response, and no ALT or AST data were exhibited. The outcome was not bracing. Only 5 out of 24 patients (20.8%) responded to the treatment. SAEs and other AEs were reported in 3 (12.5%) and in 14 (58.3%) of the patients, respectively. The data were updated at https://clinicaltrials.gov/ct2/show/results/NCT00590564 on January 15, 2016, but have not yet been published officially. According to the moderate performance of XCHT, it should not be considered as the first-line treatment in CHC patients.

TCM-700C

Compound Codyceps-TCM-700C is an herbal preparation that has been shown to be potently hepatoprotective.[71] A phase II trial was conducted to detect the effects of adding TCM-700C onto the standard combination treatment for patients with genotype 1 HCV infection. This study was completed in May 2012. Based on the data updated at the https://clinicaltrials.gov/ct2/show/study/NCT00556504 on August 7, 2014, there appeared to be no differences in SVR, virological response, and ALT response between regimens with and those without TCM-700C. SAEs were reported in 22.0% (9/41) and 14.3% (6/42) of patients with and those without TCM-700C, respectively.

Kuan Sin Yin (KSY)

Taipei City Hospital, Taiwan, conducted a phase II-III randomized, double-blinded and placebo-controlled trial to examine whether the Chinese herbal formula KSY is effective in HCV carriers with abnormal liver function. The results showed that 6 weeks of treatment with KSY significantly reduced HCV viral load, and ALT and AST levels were obviously decreased.[72] Although KSY is not effective enough to gain SVR, it shows effective hepatoprotection for CHC patients. However, the long-term effects of KSY still remain to be evaluated in the future.

Current critical issues and hurdles, and future perspectives

Thus far, a great deal of preclinical studies on the anti-HCV effects of herbal medicines have been conducted, demonstrating great effectiveness *in vitro*. However, only a few clinical trials with high methodological quality have been conducted, resulting in inconclusive findings for clinical efficacy. Thus, the exploratory journey from bench to bedside still has a long way to go. As such, the question then is, what are the critical issues and hurdles currently existing in the journey and the future perspectives?

First, different from western medicine, Chinese herbalism is based on concepts of holism and syndrome differentiation. The onset of sickness is considered as the imbalance of Yin and Yang, leading to miscellaneous symptoms in the course of disease.[73] Herbal physicians treat patients as a whole and prescribe individual formulas based on the different body habitus. However, in the clinical trials, the interventions for all the patients recruited are the same, regardless of the different body habitus, contradicting the therapeutic pillars of Chinese herbalism. It would probably shed new light on the clinical trials of herbal medicines if the patients were to be given interventions according to their body habitus; although, this practice is hard to achieve in RCTs, which are conducted according to the approaches of western medicine.

Second, for formulation selection, herbal physicians obey the principle that the selected herbs are able to work in a complementary way with other herbs in the formulas, which could improve efficacy and reduce AEs.[74,75] It is difficult to identify the actually acting compounds in the formulas. Moreover, after consumption, the herbs are metabolized in the liver, resulting in transformation of the bioactive compounds. Therefore, it is necessary to clearly define which is the "protagonist" (the naïve compound or the transformative compound) that exhibits anti-HCV activities. To achieve this, more animal experiments are required. However, currently, the ideal animal models for anti-HCV study are rare, which restricts the conduct of animal experiments. Further research is required to develop an ideal HCV animal model for anti-HCV study. Using such an HCV animal model would be of help to identify the actual acting compounds in the herbal medicines and determine the administration methods, which would contribute to the improvement of clinical efficacy and safety in clinical trials.

Conclusions

Despite apparent anti-HCV activities *in vitro*, clinical efficacy and safety of herbal medicines for the treatment of HCV infection have not been revealed convincingly. More animal studies in ideal models and well-designed clinical trials with larger sample sizes and longer treatment periods, taking the body habitus into consideration, are required to further assess the efficacy and safety of herbal medicines for HCV infection. Therefore, the exploratory journey towards treating HCV infections with herbal medicines, from bench to bedside, still has a long way to go.

Acknowledgments

This paper was supported by the Traditional Chinese Medicine Bureau of Guangdong Province (No. 20151283, to XY Yang) and the Department of Education of Guangdong Province (No. 2018GKTSCX033, to XY Yang).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Manuscript writing (XYY, YYZ), supports of administration or intellectual content (WRX, SHH, LHW, XXH), and review design and critical revision of the manuscript (HHX).

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