Review Article

A Survey of Therapeutic Effects of *Artemisia capillaris* in Liver Diseases

Eungyeong Jang,¹ Bum-Joon Kim,² Kyung-Tae Lee,³ Kyung-Soo Inn,⁴ and Jang-Hoon Lee¹

¹Department of Internal Medicine, College of Korean Medicine, Kyung Hee University, Seoul 02447, Republic of Korea

²Department of Microbiology and Immunology, Liver Research Institute, Cancer Research Institute and SNUMRC, College of Medicine, Seoul National University, Seoul 03080, Republic of Korea

³Department of Pharmaceutical Biochemistry and Department of Life and Nanopharmaceutical Science, College of Pharmacy, Kyung Hee University, Seoul 02447, Republic of Korea

⁴Department of Pharmaceutical Science, College of Pharmacy, Kyung Hee University, Seoul 02447, Republic of Korea

Correspondence should be addressed to Kyung-Soo Inn; innks@khu.ac.kr and Jang-Hoon Lee; komclive@khmc.or.kr

Received 7 May 2015; Revised 27 July 2015; Accepted 9 August 2015

Academic Editor: Yibin Feng

Copyright © 2015 Eungyeong Jang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Artemisia capillaris has been recognized as an herb with therapeutic efficacy in liver diseases and widely used as an alternative therapy in Asia. Numerous studies have reported the antisteatotic, antioxidant, anti-inflammatory, choleric, antiviral, antifibrotic, and antitumor activities of *A. capillaris*. These reports support its therapeutic potential in various liver diseases such as chronic hepatitis B virus (HBV) infection, cirrhosis, and hepatocellular carcinoma. In addition, several properties of its various constituents, which provide clues to the underlying mechanisms of its therapeutic effects, have been studied. This review describes the scientific evidence supporting the therapeutic potential of *A. capillaris* and its constituents in various liver diseases.

1. Introduction

The liver plays a vital role in the metabolic maintenance of homeostasis and toxic excretion of endogenous and exogenous metabolites such as those associated with drugs, alcohols, viral and fungal infections, and various noxious materials [1]. Because of this important hepatic function, liver impairment can induce the development of a variety of pathological and clinical conditions such as hepatic steatosis, inflammation, fibrotic change, and tumors. Although a considerable number of conventional medicines have been used for liver dysfunction, unanticipated side effects such as hepatic or renal toxicity, intolerance to drugs, and poor treatment occur in clinical settings. These limitations have led to the search for alternative remedies among the various herbal formulas. These herbal remedies have existed for a long time and have been useful in the management of hepatic diseases, and *A. capillaris* is one of the medicinal herbs that are frequently used for liver diseases [2, 3].

A. capillaris, called wormwood in English or yin chen hao in Chinese, belongs to a large genus *Artemisia*, which includes

approximately over 500 species and is part of the tribe Anthemideae of the Asteraceae family [4]. *A. capillaris* has been widely used as an alternative medicinal herb since ancient times to improve conditions such as pyrexia, pain, hepatotoxicity, inflammation, cholestasis, and jaundice [5]. Currently, a number of constituents including *p*-hydroxyacetophenone, β -sitosterol, scoparone, cirsimaritin, quercetin, arcapillin, capillin, 6,7-dimethylesculetin, 6,7-dimethoxycoumarin, capillone, capillarin, 4'-methyl capillarisin, cirsilineol, cirsimaritin, and capillarisin from *A. capillaris* have been shown to have antihepatofibrotic, anti-inflammatory, choleric, and hepatoprotective activities [6–10]. Furthermore, more diverse pharmacological properties of *A. capillaris* have been studied in areas such as lipoapoptosis, obesity, skin cancer, antibacterial activities, and atopic dermatitis, as well as liver protection [11–15].

Despite the various medicinal applications that have been suggested for *A. capillaris* through a large number of surveys, there has been no review article that provides useful information with a well-organized collation of the pharmacological effects of *A. capillaris* and its compounds. Therefore, to meet

FIGURE 1: Schematic diagram of major effects of *A. capillaris* in order of progression of liver diseases. The lower box indicates reported therapeutic activities of *A. capillaris* related to liver pathological conditions in the upper box.

this need, we researched a wide range of studies on therapeutic activities of *A. capillaris* and its constituents in liver diseases. In addition, we arranged these results based on the key activities that occur during the pathological developmental stages from liver dysfunction to hepatocarcinogenesis (Figure 1).

2. Therapeutic Effects of *A. capillaris*

For a variety of activities from *A. capillaris* relevant to liver diseases, we organized various therapeutic effects that have been reported for this plant according to each pathological step from oxidative stress to carcinogenesis (Table 1).

2.1. Antioxidant Effects. The liver is very susceptible to oxidative stress and plays an important role in controlling the balance between the antioxidant defense system and enhanced oxidative stress [30]. Excessive production of deleterious reactive oxygen species (ROS) could lead to liver dysfunction symptoms such as steatosis [17], alcoholic degeneration [19], cholestasis [18], and fibrosis [16] as a result of hepatocellular damage. Therefore, many studies related to the antioxidant effects of *A. capillaris* in hepatotoxicity have been conducted using chemical toxins, alcohol, fatty acids, bile duct ligation, and so forth. Oxidative injury to the liver can be confirmed by monitoring the malondialdehyde (MDA), which represents lipid peroxidative products. *A. capillaris* has been shown to significantly reduce the MDA content in the liver of rats with bile duct ligation ($p < 0.5$) [18] and 50 and 100 mg/kg of its water extract notably decreased serum levels of MDA in alcohol-pyrazole-fed rats [19]. *A. capillaris* was also revealed to restore significantly reduced levels of antioxidant enzymes including superoxide dismutase (SOD), glutathione (GSH),

GSH-peroxidase (Px), GSH-reductase (Rd), and catalases (CAT) under conditions of oxidative stress in *in vivo* rat models [17–19]. Furthermore, the antioxidant potential of *A. capillaris* was shown to extend to liver fibrosis [18] and hepatoprotection [16, 17, 19, 30] by observing hydroxyproline, a mark of an increase in collagen synthesis and liver function enzymes including aspartate transaminase (AST) and alanine transaminase (ALT). Therefore, *A. capillaris* is a possible candidate agent for use in the reduction of oxidative toxicities and for hepatoprotection and in liver function recovery.

2.2. Antisteatotic Effect. The hepatic accumulation of lipids, a characteristic feature of fatty liver disease and steatohepatitis, is strongly associated with insulin resistance [31], fibrogenic activities [32], oxidative stress [33], and lipopapoptosis [13]. Therefore, alternative therapeutic options with antisteatotic activities which can prevent oxidative and apoptotic changes in liver induced by lipids are desirable. *A. capillaris* was reported to markedly decrease the accumulated fat volume in free fatty acid-treated HepG2 cells and 3T3-L1 adipocytes [13, 14]. *A. capillaris* also conspicuously improved the lipid profile including the triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels in obese rats [20]. These antilipidemic activities of *A. capillaris* can be attributed to its inhibition of apoptosis via the deactivation of phosphorylated (p) c-Jun N-terminal kinases (JNK) [13] or the increase in mitochondrial β -oxidation [14], but more studies are needed to apply it as one of the lipid-lowering agents.

2.3. Anti-Inflammatory Effects. Chronic inflammatory responses in the liver are often induced by viral infection, alcohol abuse, fat accumulation, and toxic agents. Chronic inflammation causes pathological changes in liver function and, therefore, might progress to severe problems such as liver cirrhosis or cancer [34]. For this reason, controlling acute or chronic inflammation is desirable in liver disease management. Studies identifying the anti-inflammatory effect of *A. capillaris* have mainly been conducted by evaluating the levels of inflammatory cytokines. For instance, the aqueous extract of *A. capillaris* decreased the production of tumor necrosis factor-(TNF-) α by deactivating nuclear factor kappa-light-chain enhancer of activated B-cells (NF- κ B) in both lipopolysaccharide- (LPS-) and ethanol-treated HepG2 cells [21, 22]. *A. capillaris* also suppressed secretion of proinflammatory cytokines such as interleukin- (IL-) 1β , IL- 1α , IL-6, and IL-8 from HepG2, RAW 264.7 cells, and rat liver [6, 22, 35]. In addition, cyclooxygenase- (COX-) 2 and nitric oxide were downregulated in HepG2, RAW 264.7, RGM-1, rat insulinoma, splenocytes, and liver cells [6, 21–23, 35, 36]. These immunosuppressive effects of *A. capillaris* can be beneficial for various kinds of inflammatory conditions that occur in the liver.

2.4. Antiviral Effects. Viral hepatitis has the propensity to progress and possibly aggravate to liver cirrhosis or hepatocellular carcinoma. It has been revealed as a serious public

TABLE 1: Experimental results based on key activities of *Artemisia capillaris*.

Herb names (ingredients, country)	Extracts	Type	Doses	Model	Results	References
<i>Antioxidant effects</i>						
<i>A. capillaris</i> and <i>Picrorhiza Rhizome</i> 2:1 (Korea)	Water	<i>In vivo</i>	200 mg/kg	CCl ₄ -injected rats	Liver weight↓ AST, ALT↓ Protein contents in the liver↑ Hydroxyproline↓ SOD↑ GSH-px↓	[16]
<i>A. capillaris</i> (Korea)	Water	<i>In vivo</i>	0.05, 0.1 g/kg	High-fat diet induced obese mice	CAT↓ GSH↓ TBARS↓ Carbonyl value↓ AST, ALT↓ MDA↓	[17]
<i>A. capillaris</i> (China)	Water	<i>In vivo</i>		Rats with bile duct ligation	SOD↑ GSH-Px↑ CAT↑ AST, ALT↓ ALP↓ LDH↓ ROS↓ TAC↑	[18]
<i>A. capillaris</i> (Korea)	Water	<i>In vivo</i>	50, 100 mg/kg	Alcohol-pyrazole-fed rat	GSH↑ GSH-Px↑ GSH-Rd↑ SOD↑ Catalase↑ Nrf2↑ HO1↑	[19]
<i>Antisteatotic effects</i>						
<i>A. capillaris</i> (Korea)	Ethanol	<i>In vitro</i>	100 µg/mL	FFAs-treated HepG2	Lipid accumulation↓ Mitochondrial β-oxidation↑	[13]
<i>A. capillaris</i> (Korea)		<i>In vivo</i>	100 mg/kg	C57BL/6J mice fed a high-fat diet	Fatty acid synthase↓ Glycerol-3-phosphate Dehydrogenase↓ TG↓ TC↓ LDL↓ HDL↑ SOD↑	[14]
<i>A. capillaris</i> (scoparone, Korea)		<i>In vivo</i>		High-fat diet induced obese rats		[20]
<i>Anti-inflammatory effects</i>						
<i>A. capillaris</i> (Korea)	Water	<i>In vitro</i>		RINm5F rat insulinoma cells	NO↓ NF-κB↓ Insulin release↑ iNOS↓	[21]
<i>A. capillaris</i> (Korea)	Water	<i>In vitro</i>		LPS-induced HepG2 and rat liver	COX-2↓ TNF-α↓ NF-κB↓ iNOS↓	[22]
<i>A. capillaris</i> (Korea)	Methanol	<i>In vitro</i>	10 µg/mL	Rat splenocytes	COX-2↓ TNF-α↓ IL-6↓	[23]
<i>Antiviral effects</i>						
<i>A. capillaris</i> (pumilaside A, China)	Ethanol	<i>In vitro</i>		HepG2.2.15	HBsAg↓ HBeAg↓ HBV DNA↓	[24]
<i>A. capillaris</i> (p-hydroxyacetophenone derivatives, China)		<i>In vitro</i>		HepG2.2.15	HBV DNA↓	[25]

TABLE 1: Continued.

Herb names (ingredients, country)	Extracts	Type	Doses	Model	Results	References
<i>Choleretic effects</i>						
<i>A. capillaris</i> (Japan)	Water	<i>In vivo</i>	3 mL/day	Rats	Bile flow↑	[26]
<i>A. capillaris</i> (Japan)		<i>In vivo</i>	50 mg/kg	Rats	Bile secretion↑	[8]
<i>Antifibrotic effects</i>						
<i>A. capillaris</i> (Korea)	Water	<i>In vivo</i>	50 mg/kg	Rats with bile duct ligation	α -SMA↓ PDGF- β ↓ TGF- β ↓ Col1A1↓ TIMP1↓ TIMP2↓ Collagen-1↓ α -SMA↓ Caspases 3, 9↑	[27]
<i>A. capillaris</i> (β -sitosterol, Korea)		<i>In vitro</i>	120 μ M	LX2 cells	BAX↑ Bcl-2↓ Mcl-1↓ pMEK↓ pERK↓	[7]
<i>A. capillaris</i> (β -sitosterol, Korea)		<i>In vivo</i>	40 mg/kg	DMN-induced fibrotic mouse	Collagen-1↓ α -SMA↓ PDGF- β ↓	[7]
<i>A. capillaris</i> (China)	Water	<i>In vivo</i>		CCl ₄ -induced rats	TGF- β ↓ CTGF↓	[3]
<i>Antitumor effects</i>						
<i>A. capillaris</i> (capillin, Japan)	Water	<i>In vitro</i>	2 μ M	HL-60 cells	Cell growth↓ JNK/SAPK activation Cytochrome c release	[28]
<i>A. capillaris</i> (China)	Water	<i>In vitro</i>	25~200 μ g/mL	SMMC-7721, human hepatoma cell line	Cell growth↓ G ₀ /G ₁ arrest	[29]

health problem that affects people worldwide. Despite the available conventional therapies such as nucleoside and nucleotide analogues or interferon, these agents are fraught with challenging limitations including toxicity, drug resistance, recurrence, and unsatisfactory treatment outcomes [18, 25, 37, 38]. Traditional herbal medicines, therefore, like *Rheum palmatum*, *Scutellaria baicalensis*, and *Salvia miltiorrhiza*, have also been used for the treatment of hepatitis B virus (HBV) infections [38]. In particular, previous investigations suggested that the antiviral effects of *A. capillaris* were attributable to its isolated constituents [24, 25, 39]. Pumilaside A was among a series of compounds isolated from the 90% ethanol extract of *A. capillaris* and was discovered to have the strongest antiviral effect in HepG2.2.15 cells with a half-maximal inhibitory concentration (IC₅₀) of 15.02 μ M and 111.3 (SI) for HBsAg, 9.0 μ M (IC₅₀) and 185.9 (SI) for HBeAg, and 12.01 μ M (IC₅₀) and 139.2 (SI) for HBV DNA. In addition, 19–25 compounds that inhibited viral secretions were present [24]. In addition, a recent study revealed that the compound 2f, which is a derivative of *p*-hydroxyacetophenone from *A. capillaris*, showed inhibitory effects with IC₅₀ of 5.8 μ M and SI of 160.3 against HBV DNA replication [25]. Consequently, *A. capillaris*, which contained components with antiviral activity, was thought to be an adequate therapeutic candidate for the control of viral infections of the liver, although previous studies of this plant were mostly limited to HBV infections.

2.5. Choleretic Effects. Jaundice which is one of the symptoms induced by cholestasis turns skin, conjunctival membranes, and urine yellowish and is frequently seen in liver diseases such as hepatitis, liver cirrhosis, bile duct obstruction, and cancer. A number of studies of herbal therapies for hyperbilirubinemia have focused mainly on neonatal jaundice because of the adverse effects of drug treatment and exchange transfusions [40–42]. In particular, *A. capillaris* has been used for years in China, Japan, and Korea to alleviate jaundice and its choleretic effect and was officially implemented for use in Japan from 1981 to 1994 based on its various components [8, 26, 43]. Consequently, *p*-hydroxyacetophenone, scoparone, capillartemisin B₁, and artemipillins A and C from *A. capillaris* (dried flower, 50 mg/kg) were shown to increase bile flow without affecting the enterohepatic circulation or metabolism of bile acids in rat models. A significant increase in bile secretion of 169% was observed within 30 min of the administration of *p*-hydroxyacetophenone [26]. In addition, 3 mL of bile secretion for 6–8 h after treatment with the water extract of *A. capillaris* [8] might suggest the potential therapeutic benefits of *A. capillaris* on cholestatic liver dysfunctions.

2.6. Antifibrotic Effects. Liver fibrosis is a healing process that occurs in damaged liver tissues and can progress to liver cirrhosis or carcinoma [7, 44, 45]. The accumulation of fibrotic factors like collagen-1 and α -smooth muscle actin (α -SMA)

in the liver is attributable to hepatic stellate cells induced by the tumor growth factor- (TGF-) β or platelet-derived growth factor (PDGF) [46]. However, conventional drugs that can block the progression of fibrogenesis or prevent liver fibrosis have not been developed yet. Concerning the antifibrotic effects of *A. capillaris*, there existed results effective against liver fibrosis in rat models. Han et al. demonstrated that 50 mg/kg dose of the water extract of *A. capillaris* had anti-hepatofibrotic effects in rats with bile duct ligation and regulated fibrogenic mediators such as α -SMA, PDGF- β , TGF- β , collagen, type I, alpha 1 (Col1A1), and tissue inhibitor of metalloproteinases TIMP1 and TIMP2 [27]. The water extract of *A. capillaris* also suppressed PDGF- β , TGF- β , and connective tissue growth factor (CTGF), which are three major profibrotic cytokines, in a carbon tetrachloride- (CCl_4 -) induced liver fibrosis rat model. However, the statistical significance was not proven, and *Artemisia iwayomogi* rather than *A. capillaris* was more effective against the fibrotic changes [3]. The β -sitosterol derived from *A. capillaris* administered at 120 μM and 40 mg/kg significantly regulated Col1A1 and α -SMA in LX2 cells and dimethylnitrosamine- (DMN-) induced fibrotic mice [7]. This effect was mediated by activating caspase-3, caspase-9, and Bcl-2-associated X protein (BAX) and inhibiting B-cell lymphoma 2 (Bcl-2), myeloid cell leukemia-1 (Mcl-1), phosphorylation of mitogen-activated protein kinase (MEK), and extracellular signal-regulated kinases (ERK) [7].

2.7. Antitumor Effects. Primary liver cancer originating from the liver remains a serious health problem. Although the range of the geographical distribution and incidence rates are diverse with countries, gender-wise it is more prevalent in males than in females [47]. There are numerous reports on the various antitumor effects of curative treatment options like chemicals, proton, and immune therapy [48, 49]. Most studies of the inhibitory effect of *A. capillaris* against hepatoma cells have focused on apoptotic effects. Articles in Taiwan and China reported that *A. capillaris* showed growth-inhibitory effects in SMMC-7721 (human hepatoma cell line), HepG2, Huh-7, HeLa, and mouse liver cells by inducing tumor cell apoptosis [29, 50, 51]. These results are opposed to the inhibition of TGF- β_1 induced apoptosis [52], but *A. capillaris* prevented apoptotic morphological changes of normal hepatocytes, not tumor cells in this study. Moreover, *A. capillaris* was also found to promote the apoptotic process in cancer cells like the human leukemia HL-60 cells or nasopharyngeal carcinoma cells (CNE-2 cells), even though they are not related to the liver [28, 53]. In view of these results, intensive studies are required to expand the possible application of the antitumor effects of *A. capillaris* to other forms of cancer.

3. Medicinal Effects of Various Constituents of *A. capillaris*

There are a number of substances isolated from *A. capillaris*, which exhibit diverse medicinal effects applicable to different liver-related diseases (Table 2). Among those bioactive constituents, 6 compounds with remarkable medicinal effects were selected and discussed (Figures 2 and 3).

3.1. Capillin. Capillin, the most active and major substance found in *A. capillaris*, upregulated the apoptotic processes and thereby induced antitumor effects in human leukemia HL-60 cells by splitting DNA and activating the JNK/stress-activated protein kinases (SAPK) pathway. IC_{50} value for tumor-suppressive activity of capillin was $6.5 \pm 2.9 \mu\text{M}$, which was 7.6- to 30-fold lower than those of capillin ($134.9 \pm 16.4 \mu\text{M}$), capillarisin ($49.3 \pm 12.2 \mu\text{M}$), and 6,7-dimethylesculetin ($197.4 \pm 17.5 \mu\text{M}$), indicating its strong growth-inhibitory activity [28]. Capillin (1–10 μM) from *Artemisia monosperma* also had cytotoxic and proapoptotic effects on four human tumor cells including colon, pancreatic, lung, and larynx carcinomas [59].

3.2. Scoparone. Scoparone, a derivative of 6,7-dimethoxycoumarin (coumarin) isolated from *A. capillaris*, showed antioxidant properties by reducing the MDA and ALT levels in cold-reserved rat hepatocytes, thereby preventing ischemic injury induced by liver transplantation [56]. The anti-inflammatory activities of scoparone were revealed by its inhibition of the expression of IL-8, monocyte chemotactic protein-1, and NF- κB subunits via I- $\kappa\text{B}\alpha$ activation in U 937 human monocytes [75]. Therefore, scoparone could be a potential candidate for the therapy of hepatitis or biliary tract infection [57].

3.3. Scopoletin. There are several reports of the antioxidant effects of scopoletin extracted from *Evolvulus alsinoides* and *Aegle marmelos* leaves. In addition, scopoletin from the ethyl acetate fraction of *A. capillaris* was found to have antioxidant potentials mediated by reducing the overaccumulation of ROS [17]. Scopoletin from *A. iwayomogi* also significantly promoted hepatic SOD, GSH-Px, and CAT activities in alcohol-induced obese rats [62]. In lipid metabolism, scopoletin effectively regulated hepatic lipogenic enzymes such as fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), glucose-6-phosphate dehydrogenase (G6PD), and phosphatidic acid phosphatase (PAP) and decreased TG in the liver by activating adenosine monophosphate- (AMP-) activated protein kinase (AMPK) and deactivating sterol regulatory element-binding transcription factor- (SREBP-) 1c in obese rats [62]. Scopoletin from *Erycibe obtusifolia* was mainly investigated for its suppression of IL-6 in LPS-induced RAW 264.7 cells [75] and fibroblast-like synoviocytes treated with IL-1 β for rheumatoid arthritis [63]. The anticancer potential of scopoletin isolated from *Gelsemium sempervirens* was shown in 7,12-dimethylbenz(α)anthracene- (DMBA-) induced skin cancer in mice and was mediated by decreasing aryl hydrocarbon receptor (AhR), cytochrome P450 (CYP) 1A1, proliferating cell nuclear antigen (PCNA), signal transducer and activator of transcription-3 (Stat-3), survivin, matrix metalloproteinase-2 (MMP-2), cyclin D1, and c-myc mediators of carcinogenesis [65].

3.4. Chlorogenic Acids. Chlorogenic acid is a polyphenolic substance isolated from the methanol extracts of *A. capillaris* spectrophotometrically [68]. A previous study indicated that there was also a large amount of chlorogenic acid in the water extracts of *A. capillaris* using ultra-high-performance

TABLE 2: Various effects of constituents isolated and derived from *Artemisia capillaris*.

Compounds	Plants	Effects	References
Scoparone	<i>A. capillaris</i>	Vascular dilatory action	[10]
	<i>A. capillaris</i>	Choleretic	[8, 43, 54]
	<i>Artemisia scoparia</i>	Antihypertensive	[55]
	<i>A. capillaris</i>	Antioxidant	[56]
	<i>A. capillaris</i>	Anti-inflammatory	[57]
Capillartemisin	<i>A. capillaris</i>	Choleretic	[8, 58]
Capillarisin	<i>A. capillaris</i>	Antitumor	[51]
Capillin	<i>A. capillaris</i>	Anti-inflammatory	[52]
	<i>A. capillaris</i>	Antitumor	[28]
	<i>Artemisia monosperma</i>	Antitumor	[59]
Scopoletin	<i>A. capillaris</i>	Choleretic	[8]
	<i>Evolvulus alsinoides</i> L.	Antioxidant	[60]
	<i>Aegle marmelos</i> leaves	Antioxidant	[61]
	<i>A. capillaris</i>	Antioxidant	[17]
	<i>A. iwayomogi</i>	Antisteatotic	[62]
	<i>Erycibe obtusifolia</i>	Anti-inflammatory	[63, 64]
	<i>Gelsemium sempervirens</i>	Antitumor	[65]
	<i>Lycium barbarum</i>	Antitumor	[66]
Isoscapoletin	<i>A. capillaris</i>	Choleretic	[8]
Artepillin	<i>A. capillaris</i>	Choleretic	[8]
<i>p</i> -Hydroxyacetophenone	<i>A. capillaris</i>	Choleretic	[8]
Esculetin	Unknown	Choleretic	[67]
Chlorogenic	<i>A. capillaris</i>	Antioxidant	[68]
	<i>Phyllostachys edulis</i>	Antioxidant	[69]
	<i>A. capillaris</i>	Antioxidant	[19]
Isochlorogenic acid (= dicaffeoylquinic acid)	<i>A. capillaris</i>	Antioxidant	[68]
	<i>Laggetra alata</i>	Antiviral and antioxidant	[70]
	<i>Laggetra alata</i>	Anti-inflammatory	[71]
	<i>Crassocephalum crepidioides</i>	Antitumor	[72]
β -Sitosterol	<i>A. capillaris</i>	Antifibrotic	[7]
Quercetin	Chemical agents	Antitumor	[73]
Umbelliferone	Chemical agents	Antisteatotic	[74]
Pumilaside A	<i>A. capillaris</i>	Antiviral	[24]

liquid chromatography- (UHPLC-) mass spectrometry (MS) analysis [19]. This purified compound showed an antioxidant activity comparable to α -tocopherol in scavenging of free radicals [68] and decreased the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical in HepG2 cells [19].

3.5. Isochlorogenic Acids. Isochlorogenic acids isolated from *Laggetra alata* significantly inhibited the expressions of HBsAg, HBeAg, and cccDNA but not HBV DNA levels and induced heme oxygenase-1, a repressor of HBV replication, in HepG2.2.15 cells [54]. This result indicates that isochlorogenic acids may act at the translational and not transcriptional step of viral proliferation [70]. In addition, they showed anti-inflammatory effects, which were mediated by increasing

antioxidant enzymes like SOD and GSH-Px [68, 71]. Furthermore, the antitumor effect of isochlorogenic acids was investigated by inducing apoptosis in murine sarcoma 180 cells via the activation of NF- κ B signaling and production of nitric oxide [72].

3.6. Capillarisin. Capillarisin (5,7-dihydroxy-2-4-hydroxyphenoxy-6-methoxychromen-4-hydroxyphenoxy), the most important chromone in *A. capillaris*, was suggested to possess a potent antitumor effect shown by its suppression of the growth of HepG2, Huh-7, and mouse liver cells. Furthermore, supercritical CO₂ extraction of capillarisin had more remarkable effect than Soxhlet solvent in aspect of both purity value and IC₅₀, which implied the importance of extraction method [51].

FIGURE 2: Chemical structures of selected compounds with therapeutic effects on liver diseases.

FIGURE 3: Constituents of *A. capillaris* effective to each progressive stage of liver disease.

4. Conclusion

A. capillaris has a wide spectrum of pharmacologically effective constituents for various liver diseases ranging from fatty liver disease to liver cancer. Our findings provided at least partial and plausible explanations of the therapeutic properties of *A. capillaris* that are applicable in liver diseases. In particular, various compounds isolated from *A. capillaris* are beneficial for treating liver diseases including scoparone, scopoletin, chlorogenic acid, isochlorogenic acid, and umbelliferone. These constituents are effective for liver dysfunctions like fatty liver. In addition, scoparone, scopoletin, isochlorogenic acid, and pumilaside A are effective for hepatitis including steatohepatitis, alcoholic hepatitis, and viral hepatitis. Furthermore, scoparone, capillartemisin, capillarisin, scopoletin, isoscapoletin, artepillin, *p*-hydroxyacetophenone, esculetin, and β -sitosterol are effective for liver cirrhosis while scoparone, capillartemisin, capillarisin, capillin, scopoletin, isoscapoletin, artepillin, *p*-hydroxyacetophenone, esculetin, isochlorogenic acid, and quercetin are effective in liver cancer (Figure 3). In addition, Yin-Chen-Hao-Tang decoction including *A. capillaris* significantly

decreased α -SMA, TGF- β_1 , and procollagen 1 by suppressing apoptosis in rats with hepatic fibrosis [76, 77]. Therefore, studies elucidating the pharmacological effects of *A. capillaris* in liver diseases are required. Hence, more studies considering diverse extraction methods, experiment techniques, efficient dosage, and related metabolism are required to verify pharmacological effects of *A. capillaris*, its constituents, and decoction in liver diseases.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (Grant no. HI14C0955).

References

- [1] A. D. Kshirsagar, R. Mohite, A. S. Aggrawal, and U. R. Suralkar, "Hepato-protective medicinal plants of Ayurveda: a review," *Asian Journal of Pharmaceutical and Clinical Research*, vol. 4, no. 3, pp. 1–8, 2011.
- [2] H. Sahoo, F. Toppo, A. Bhaiji, B. Rath, and R. Sagar, "A comprehensive review on herbal drugs for hepatoprotection of 21 st Century," *International Journal of Nutrition, Pharmacology, Neurological Diseases*, vol. 4, no. 4, p. 191, 2014.
- [3] J.-H. Wang, M.-K. Choi, J.-W. Shin, S.-Y. Hwang, and C.-G. Son, "Antifibrotic effects of *Artemisia capillaris* and *Artemisia iwayomogi* in a carbon tetrachloride-induced chronic hepatic fibrosis animal model," *Journal of Ethnopharmacology*, vol. 140, no. 1, pp. 179–185, 2012.
- [4] K. S. Bora and A. Sharma, "The genus *Artemisia*: a comprehensive review," *Pharmaceutical Biology*, vol. 49, no. 1, pp. 101–109, 2011.
- [5] J.-D. Cha, M.-R. Jeong, S.-I. Jeong et al., "Chemical composition and antimicrobial activity of the essential oils of *Artemisia scoparia* and *A. capillaris*," *Planta Medica*, vol. 71, no. 2, pp. 186–190, 2005.
- [6] I. J. Seon, Y.-J. Kim, W.-Y. Lee et al., "Scoparone from *Artemisia capillaris* inhibits the release of inflammatory mediators in RAW 264.7 cells upon stimulation cells by interferon- γ plus LPS," *Archives of Pharmacol Research*, vol. 28, no. 2, pp. 203–208, 2005.
- [7] K.-S. Kim, H. J. Yang, J.-Y. Lee et al., "Effects of β -sitosterol derived from *Artemisia capillaris* on the activated human hepatic stellate cells and dimethylnitrosamine-induced mouse liver fibrosis," *BMC Complementary and Alternative Medicine*, vol. 14, no. 1, article 363, 2014.
- [8] I. Okuno, K. Uchida, M. Nakamura, and K. Sakurawi, "Studies on choleric constituents in *Artemisia capillaris* Thunb," *Chemical and Pharmaceutical Bulletin*, vol. 36, no. 2, pp. 769–775, 1988.
- [9] T. Xie, J.-Y. Liang, and J. Liu, "Research progress of *Artemisia scoparia* and *Artemisia capillaris* on chemical constituents and pharmacological effect," *Strait Pharmaceutical Journal*, vol. 16, pp. 8–13, 2004.
- [10] J. Yamahara, G. Kobayashi, H. Matsuda, T. Katayama, and H. Fujimura, "Vascular dilatory action of *Artemisia capillaris* bud extracts and their active constituent," *Journal of Ethnopharmacology*, vol. 26, no. 2, pp. 129–136, 1989.
- [11] C. Yang, D.-H. Hu, and Y. Feng, "Antibacterial activity and mode of action of the *Artemisia capillaris* essential oil and its constituents against respiratory tract infection-causing pathogens," *Molecular Medicine Reports*, vol. 11, no. 4, pp. 2852–2860, 2015.
- [12] Y. S. Kim, K. N. Bahn, C. K. Hah, H. I. Gang, and Y. L. Ha, "Inhibition of 7,12-dimethylbenz[a]anthracene induced mouse skin carcinogenesis by *Artemisia capillaris*," *Journal of Food Science*, vol. 73, no. 1, pp. T16–T20, 2008.
- [13] E. Jang, M.-H. Shin, K.-S. Kim et al., "Anti-lipoapoptotic effect of *Artemisia capillaris* extract on free fatty acids-induced HepG2 cells," *BMC Complementary and Alternative Medicine*, vol. 14, article 253, 2014.
- [14] J.-H. Hong, E.-Y. Hwang, H.-J. Kim, Y.-J. Jeong, and I. S. Lee, "*Artemisia capillaris* inhibits lipid accumulation in 3T3-L1 adipocytes and obesity in C57BL/6J mice fed a high fat diet," *Journal of Medicinal Food*, vol. 12, no. 4, pp. 736–745, 2009.
- [15] H. Ha, H. Lee, C. S. Seo et al., "*Artemisia capillaris* inhibits atopic dermatitis-like skin lesions in *Dermatophagoides farinae*-sensitized Nc/Nga mice," *BMC Complementary and Alternative Medicine*, vol. 14, no. 1, article 100, 2014.
- [16] H. S. Lee, H. H. Kim, and S. K. Ku, "Hepatoprotective effects of *Artemisia capillaris* herba and *picrorrhiza* rhizoma combinations on carbon tetrachloride-induced subacute liver damage in rats," *Nutrition Research*, vol. 28, no. 4, pp. 270–277, 2008.
- [17] J. H. Hong and I. S. Lee, "Effects of *Artemisia capillaris* ethyl acetate fraction on oxidative stress and antioxidant enzyme in high-fat diet induced obese mice," *Chemico-Biological Interactions*, vol. 179, no. 2–3, pp. 88–93, 2009.
- [18] C.-S. He, H.-Y. Yue, J. Xu et al., "Protective effects of capillary artemisia polysaccharide on oxidative injury to the liver in rats with obstructive jaundice," *Experimental and Therapeutic Medicine*, vol. 4, no. 4, pp. 645–648, 2012.
- [19] M.-K. Choi, J.-M. Han, H.-G. Kim et al., "Aqueous extract of *Artemisia capillaris* exerts hepatoprotective action in alcohol-pyrazole-fed rat model," *Journal of Ethnopharmacology*, vol. 147, no. 3, pp. 662–670, 2013.
- [20] D. W. Lim, Y. T. Kim, Y.-J. Jang, Y.-E. Kim, and D. Han, "Anti-obesity effect of *Artemisia capillaris* extracts in high-fat diet-induced obese rats," *Molecules*, vol. 18, no. 8, pp. 9241–9252, 2013.
- [21] E.-K. Kim, K.-B. Kwon, M.-J. Han et al., "Inhibitory effect of *Artemisia capillaris* extract on cytokine-induced nitric oxide formation and cytotoxicity of RINm5F cells," *International Journal of Molecular Medicine*, vol. 19, no. 3, pp. 535–540, 2007.
- [22] S. H. Hong, S. H. Seo, J. H. Lee, and B. T. Choi, "The aqueous extract from *Artemisia capillaris* Thunb. inhibits lipopolysaccharide-induced inflammatory response through preventing NF- κ B activation in human hepatoma cell line and rat liver," *International Journal of Molecular Medicine*, vol. 13, no. 5, pp. 717–720, 2004.
- [23] H.-J. Lee, T. Zerlin, Y.-H. Song, B.-E. Lee, and H.-Y. Song, "Immunomodulation potential of *Artemisia capillaris* extract in rat splenocytes," *International Journal of Phytomedicine*, vol. 5, no. 3, pp. 356–361, 2013.
- [24] Y. Zhao, C.-A. Geng, C.-L. Sun et al., "Polyacetylenes and anti-hepatitis B virus active constituents from *Artemisia capillaris*," *Fitoterapia*, vol. 95, pp. 187–193, 2014.
- [25] Y. Zhao, C. A. Geng, H. Chen et al., "Isolation, synthesis and anti-hepatitis B virus evaluation of p-hydroxyacetophenone derivatives from *Artemisia capillaris*," *Bioorganic & Medicinal Chemistry Letters*, vol. 25, no. 7, pp. 1509–1514, 2015.
- [26] I. Okuno, K. Uchida, M. Kadowaki, and A. Akahori, "Choleric effect of *Artemisia capillaris* extract in rats," *Japanese Journal of Pharmacology*, vol. 31, no. 5, pp. 835–838, 1981.
- [27] J.-M. Han, H.-G. Kim, M.-K. Choi et al., "*Artemisia capillaris* extract protects against bile duct ligation-induced liver fibrosis in rats," *Experimental and Toxicologic Pathology*, vol. 65, no. 6, pp. 837–844, 2013.
- [28] Y. Masuda, K. Asada, R. Satoh, K. Takada, and J. Kitajima, "Capillin, a major constituent of *Artemisia capillaris* Thunb. flower essential oil, induces apoptosis through the mitochondrial pathway in human leukemia HL-60 cells," *Phytomedicine*, vol. 22, no. 5, pp. 545–552, 2015.
- [29] Y. Q. Hu, R. X. Tan, M. Y. Chu, and J. Zhou, "Apoptosis in human hepatoma cell line SMMC-7721 induced by water-soluble macromolecular components of *Artemisia capillaris* Thunberg," *Japanese Journal of Cancer Research*, vol. 91, no. 1, pp. 113–117, 2000.

- [30] A. H. Gilani, S. Yaeesh, Q. Jamal, and M. N. Ghayur, "Hepatoprotective activity of aqueous-methanol extract of *Artemisia vulgaris*," *Phytotherapy Research*, vol. 19, no. 2, pp. 170–172, 2005.
- [31] C. A. Nagle, E. L. Klett, and R. A. Coleman, "Hepatic triacylglycerol accumulation and insulin resistance," *Journal of Lipid Research*, vol. 50, supplement, pp. S74–S79, 2009.
- [32] H. Wobser, C. Dorn, T. S. Weiss et al., "Lipid accumulation in hepatocytes induces fibrogenic activation of hepatic stellate cells," *Cell Research*, vol. 19, no. 8, pp. 996–1005, 2009.
- [33] A. E. M. Vickers, "Characterization of hepatic mitochondrial injury induced by fatty acid oxidation inhibitors," *Toxicologic Pathology*, vol. 37, no. 1, pp. 78–88, 2009.
- [34] L. A. Zenewicz, G. D. Yancopoulos, D. M. Valenzuela, A. J. Murphy, M. Karow, and R. A. Flavell, "Interleukin-22 but not interleukin-17 provides protection to hepatocytes during acute liver inflammation," *Immunity*, vol. 27, no. 4, pp. 647–659, 2007.
- [35] J. Park, K. Hahm, S. Kwon, and E. Kim, "The anti-inflammatory effects of acidic polysaccharide from *artemisia capillaris* on *Helicobacter pylori* infection," *Journal of Cancer Prevention*, vol. 18, no. 2, pp. 161–168, 2013.
- [36] J.-D. Cha, S.-E. Moon, H.-Y. Kim, J.-C. Lee, and K.-Y. Lee, "The essential oil isolated from *Artemisia capillaris* prevents LPS-induced production of NO and PGE₂ by inhibiting MAPK-mediated pathways in raw 264.7 macrophages," *Immunological Investigations*, vol. 38, no. 6, pp. 483–497, 2009.
- [37] E. Tsega, "Epidemiology, prevention and treatment of viral hepatitis with emphasis on new developments," *Ethiopian Medical Journal*, vol. 38, no. 2, pp. 131–141, 2000.
- [38] Y. Chen and J. Zhu, "Anti-HBV effect of individual traditional Chinese herbal medicine in vitro and in vivo: an analytic review," *Journal of Viral Hepatitis*, vol. 20, no. 7, pp. 445–452, 2013.
- [39] Y. Zhao, C.-A. Geng, Y.-B. Ma et al., "UFLC/MS-IT-TOF guided isolation of anti-HBV active chlorogenic acid analogues from *Artemisia capillaris* as a traditional Chinese herb for the treatment of hepatitis," *Journal of Ethnopharmacology*, vol. 156, pp. 147–154, 2014.
- [40] L. Kassem, M. Abdelrahim, and H. Naguib, "Investigating the efficacy and safety of silymarin in management of hyperbilirubinemia in neonatal jaundice," *Medicine Science—International Medical Journal*, vol. 2, no. 2, pp. 575–590, 2013.
- [41] C. Y. Yeung, C. S. Leung, and Y. Z. Chen, "An old traditional herbal remedy for neonatal jaundice with a newly identified risk," *Journal of Paediatrics and Child Health*, vol. 29, no. 4, pp. 292–294, 1993.
- [42] T. F. Fok, "Neonatal jaundice—traditional Chinese medicine approach," *Journal of Perinatology*, vol. 21, supplement 1, pp. S98–S107, 2001.
- [43] T. Ikenaga, M. Hizako, M. Tajima, and K. Nakashima, "Production of choleric substances in the capitulum, leaf and stem of *Artemisia capillaris* during the plant growth cycle," *Biological and Pharmaceutical Bulletin*, vol. 17, no. 1, pp. 150–151, 1994.
- [44] S. L. Friedman, "Liver fibrosis—from bench to bedside," *Journal of Hepatology*, vol. 38, supplement 1, pp. S38–S53, 2003.
- [45] J. P. Iredale, "Cirrhosis: new research provides a basis for rational and targeted treatments," *British Medical Journal*, vol. 327, no. 7407, pp. 143–147, 2003.
- [46] S. L. Friedman, "Evolving challenges in hepatic fibrosis," *Nature Reviews Gastroenterology and Hepatology*, vol. 7, no. 8, pp. 425–436, 2010.
- [47] F. X. Bosch, J. Ribes, M. Díaz, and R. Cléries, "Primary liver cancer: worldwide incidence and trends," *Gastroenterology*, vol. 127, pp. S5–S16, 2004.
- [48] T. F. Greten, X. W. Wang, and F. Korangy, "Current concepts of immune based treatments for patients with HCC: from basic science to novel treatment approaches," *Gut*, vol. 64, no. 5, pp. 842–848, 2015.
- [49] F. Dionisi and M. Amichetti, "Proton therapy results in the treatment of hepatocellular carcinoma according to the barcelona-clinic liver cancer (BCLC) staging system," *International Journal of Medical Physics, Clinical Engineering and Radiation Oncology*, vol. 04, no. 02, pp. 96–103, 2015.
- [50] T. Kosuge, M. Yokota, K. Sugiyama, T. Yamamoto, M. Y. Ni, and S. C. Yan, "Studies on antitumor activities and antitumor principles of Chinese herbs. I. Antitumor activities of Chinese herbs," *Yakugaku Zasshi*, vol. 105, no. 8, pp. 791–795, 1985.
- [51] C.-C. Yang, M.-R. Lee, S.-L. Hsu, and C.-M. J. Chang, "Super-critical fluids extraction of capillarisin from *Artemisia capillaris* and its inhibition of in vitro growth of hepatoma cells," *The Journal of Supercritical Fluids*, vol. 42, no. 1, pp. 96–103, 2007.
- [52] M. Yamamoto, K. Ogawa, M. Morita, K. Fukuda, and Y. Komatsu, "The herbal medicine Inchin-ko-to inhibits liver cell apoptosis induced by transforming growth factor β 1," *Hepatology*, vol. 23, no. 3, pp. 552–559, 1996.
- [53] G. Feng, X. Wang, C. You et al., "Antiproliferative potential of *Artemisia capillaris* polysaccharide against human nasopharyngeal carcinoma cells," *Carbohydrate Polymers*, vol. 92, no. 2, pp. 1040–1045, 2013.
- [54] M. Aburada, H. Sasaki, and M. Harada, "Pharmacological studies of *Gardeniae fructus*. II. Contribution of the constituent crude drugs to choleric activity of 'Inchinko-to' in rats (author's transl)," *Yakugaku Zasshi*, vol. 96, no. 2, pp. 147–153, 1976.
- [55] K. S. Jamwal, M. L. Sharma, N. Chandhoke, and B. J. Ghatak, "Pharmacological action of 6,7-dimethoxy coumarin (Scoparone) isolated from *Artemisia scoparia*, Waldst & Kit," *The Indian Journal of Medical Research*, vol. 60, no. 5, pp. 763–771, 1972.
- [56] H. R. Cho, D. H. Choi, B. K. Ko et al., "Cold preservation of rat cultured hepatocytes: the scoparone effect," *Transplantation Proceedings*, vol. 32, no. 7, pp. 2325–2327, 2000.
- [57] S. I. Jang, Y.-J. Kim, H. J. Kim et al., "Scoparone inhibits PMA-induced IL-8 and MCP-1 production through suppression of NF- κ B activation in U937 cells," *Life Sciences*, vol. 78, no. 25, pp. 2937–2943, 2006.
- [58] I. Kitagawa, Y. Fukuda, M. Yoshihara, J. Yamahara, and M. Yoshikawa, "Capillartemisin A and B, two new choleric principles from *Artemisia capillaris* Herba," *Chemical and Pharmaceutical Bulletin*, vol. 31, no. 1, pp. 352–355, 1983.
- [59] L. C. Whelan and M. F. Ryan, "Effects of the polyacetylene capillin on human tumour cell lines," *Anticancer Research*, vol. 24, no. 4, pp. 2281–2286, 2004.
- [60] F. Cervenka, V. Koleckar, Z. Rehakova et al., "Evaluation of natural substances from *Evolvulus alsinoides* L. with the purpose of determining their antioxidant potency," *Journal of Enzyme Inhibition and Medicinal Chemistry*, vol. 23, no. 4, pp. 574–578, 2008.
- [61] S. Panda and A. Kar, "Evaluation of the antithyroid, antioxidative and antihyperglycemic activity of scopoletin from *Aegle marmelos* leaves in hyperthyroid rats," *Phytotherapy Research*, vol. 20, no. 12, pp. 1103–1105, 2006.

- [62] H.-I. Lee, K. W. Yun, K.-I. Seo, M.-J. Kim, and M.-K. Lee, "Scopoletin prevents alcohol-induced hepatic lipid accumulation by modulating the AMPK-SREBP pathway in diet-induced obese mice," *Metabolism*, vol. 63, no. 4, pp. 593–601, 2014.
- [63] R. Pan, X.-H. Gao, Y. Li, Y.-F. Xia, and Y. Dai, "Anti-arthritis effect of scopoletin, a coumarin compound occurring in *Erycibe obtusifolia* Benth stems, is associated with decreased angiogenesis in synovium," *Fundamental and Clinical Pharmacology*, vol. 24, no. 4, pp. 477–490, 2010.
- [64] Y. Dou, B. Tong, Z. Wei, Y. Li, Y. Xia, and Y. Dai, "Scopoletin suppresses IL-6 production from fibroblast-like synoviocytes of adjuvant arthritis rats induced by IL-1 β stimulation," *International Immunopharmacology*, vol. 17, no. 4, pp. 1037–1043, 2013.
- [65] S. S. Bhattacharyya, S. Paul, S. Dutta, N. Boujedaini, and A. R. Khuda-Bukhsh, "Anti-oncogenic potentials of a plant coumarin (7-hydroxy-6-methoxy coumarin) against 7,12-dimethylbenz [a] anthracene-induced skin papilloma in mice: the possible role of several key signal proteins," *Zhong Xi Yi Jie He Xue Bao*, vol. 8, no. 7, pp. 645–654, 2010.
- [66] X.-L. Liu, L. Zhang, X.-L. Fu, K. Chen, and B.-C. Qian, "Effect of scopoletin on PC3 cell proliferation and apoptosis," *Acta Pharmacologica Sinica*, vol. 22, no. 10, pp. 929–933, 2001.
- [67] T. Komiya, Y. Naruse, and H. Oshio, "Studies on 'Inchinko'. II. Studies on the compounds related to capillarisin and flavonoids (author's transl)," *Yakugaku Zasshi*, vol. 96, no. 7, pp. 855–862, 1976.
- [68] H.-C. Seo, M. Suzuki, M. Ohnishi-Kameyama et al., "Extraction and identification of antioxidant components from *Artemisia capillaris* herba," *Plant Foods for Human Nutrition*, vol. 58, no. 3, pp. 1–12, 2003.
- [69] M.-H. Kweon, H.-J. Hwang, and H.-C. Sung, "Identification and antioxidant activity of novel chlorogenic acid derivatives from bamboo (*Phyllostachys edulis*)," *Journal of Agricultural and Food Chemistry*, vol. 49, no. 10, pp. 4646–4655, 2001.
- [70] B.-J. Hao, Y.-H. Wu, J.-G. Wang et al., "Hepatoprotective and antiviral properties of isochlorogenic acid A from *Lagdera alata* against hepatitis B virus infection," *Journal of Ethnopharmacology*, vol. 144, no. 1, pp. 190–194, 2012.
- [71] Y. Wu, C. Zhou, L. Song et al., "Effect of total phenolics from *Lagdera alata* on acute and chronic inflammation models," *Journal of Ethnopharmacology*, vol. 108, no. 2, pp. 243–250, 2006.
- [72] K. Tomimori, S. Nakama, R. Kimura, K. Tamaki, C. Ishikawa, and N. Mori, "Antitumor activity and macrophage nitric oxide producing action of medicinal herb, *Crassocephalum crepidioides*," *BMC Complementary and Alternative Medicine*, vol. 12, no. 1, article 78, 2012.
- [73] E. Angst, J. L. Park, A. Moro et al., "The flavonoid quercetin inhibits pancreatic cancer growth in vitro and in vivo," *Pancreas*, vol. 42, no. 2, pp. 223–229, 2013.
- [74] M.-J. Kim, M.-O. Sim, H.-I. Lee, J. R. Ham, K.-I. Seo, and M.-K. Lee, "Dietary umbelliferone attenuates alcohol-induced fatty liver via regulation of PPAR α and SREBP-1c in rats," *Alcohol*, vol. 48, no. 7, pp. 707–715, 2014.
- [75] E. P. Sabina, S. Chandel, and M. K. Rasool, "Inhibition of monosodium urate crystal-induced inflammation by withaferin A," *Journal of Pharmacy and Pharmaceutical Sciences*, vol. 11, no. 4, pp. 46–55, 2008.
- [76] T.-Y. Lee, H.-H. Chang, J.-H. Chen, M.-L. Hsueh, and J.-J. Kuo, "Herb medicine Yin-Chen-Hao-Tang ameliorates hepatic fibrosis in bile duct ligation rats," *Journal of Ethnopharmacology*, vol. 109, no. 2, pp. 318–324, 2007.
- [77] T.-Y. Lee, H.-H. Chang, M.-Y. Wu, and H.-C. Lin, "Yin-Chen-Hao-Tang ameliorates obstruction-induced hepatic apoptosis in rats," *Journal of Pharmacy and Pharmacology*, vol. 59, no. 4, pp. 583–590, 2007.