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**EDITORIAL**

- 3379 Follow-up after curative resection for gastric cancer: Is it time to tailor it?

*Aurello P, Petrucciani N, Antolino L, Giulitti D, D'Angelo F, Ramacciato G*

- 3388 Cautiously using natural medicine to treat liver problems

*Xiong F, Guan YS*

**REVIEW**

- 3396 Renin angiotensin system in liver diseases: Friend or foe?

*Simões e Silva AC, Miranda AS, Rocha NP, Teixeira AL*

- 3407 Relationship between adipose tissue dysfunction, vitamin D deficiency and the pathogenesis of non-alcoholic fatty liver disease

*Cimini FA, Barchetta I, Carotti S, Bertocchini L, Baroni MG, Vespasiani-Gentilucci U, Cavallo MG, Morini S*

- 3418 Recent advances in the management of pruritus in chronic liver diseases

*Tajiri K, Shimizu Y*

**ORIGINAL ARTICLE**

**Basic Study**

- 3427 Oxidative stress-induced mitochondrial dysfunction in a normal colon epithelial cell line

*Packiriswamy N, Coulson KF, Holcombe SJ, Sordillo LM*

- 3440 Role of AXL in invasion and drug resistance of colon and breast cancer cells and its association with p53 alterations

*Abdel-Rahman WM, Al-khayyal NA, Nair VA, Aravind SR, Saber-Ayad M*

- 3449 Effects of heme oxygenase-1-modified bone marrow mesenchymal stem cells on microcirculation and energy metabolism following liver transplantation

*Yang L, Shen ZY, Wang RR, Yin ML, Zheng WP, Wu B, Liu T, Song HL*

- 3468 Diabetes recurrence after metabolic surgeries correlates with re-impaired insulin sensitivity rather than beta-cell function

*Liu T, Zhong MW, Liu Y, Sun D, Wei M, Huang X, Cheng YG, Wu QZ, Wu D, Zhang XQ, Wang KX, Hu SY, Liu SZ*

**Case Control Study**

- 3480 Polymorphisms of microRNA target genes *IL12B*, *INSR*, *CCND1* and *IL10* in gastric cancer  
*Petkevicius V, Salteniene V, Juzenas S, Wex T, Link A, Leja M, Steponaitiene R, Skieceviene J, Kupcinskas L, Jonaitis L, Kiudelis G, Malfertheiner P, Kupcinskas J*

- 3488 Insulin-like growth factor-1, IGF binding protein-3, and the risk of esophageal cancer in a nested case-control study  
*Adachi Y, Nojima M, Mori M, Yamashita K, Yamano H, Nakase H, Endo T, Wakai K, Sakata K, Tamakoshi A*

**Retrospective Cohort Study**

- 3496 Tumor-associated autoantibodies are useful biomarkers in immunodiagnosis of  $\alpha$ -fetoprotein-negative hepatocellular carcinoma  
*Wang T, Liu M, Zheng SJ, Bian DD, Zhang JY, Yao J, Zheng QF, Shi AM, Li WH, Li L, Chen Y, Wang JH, Duan ZP, Dong L*

**Observational Study**

- 3505 Clinical course of ulcerative colitis patients who develop acute pancreatitis  
*Kim JW, Hwang SW, Park SH, Song TJ, Kim MH, Lee HS, Ye BD, Yang DH, Kim KJ, Byeon JS, Myung SJ, Yang SK*
- 3513 Relationship between use of selective serotonin reuptake inhibitors and irritable bowel syndrome: A population-based cohort study  
*Lin WZ, Liao YJ, Peng YC, Chang CH, Lin CH, Yeh HZ, Chang CS*
- 3522 Laparoscopic management of gastric gastrointestinal stromal tumors: A retrospective 10-year single-center experience  
*Liao GQ, Chen T, Qi XL, Hu YF, Liu H, Yu J, Li GX*

**Prospective Study**

- 3530 Short health scale: A valid measure of health-related quality of life in Korean-speaking patients with inflammatory bowel disease  
*Park SK, Ko BM, Goong HJ, Seo JY, Lee SH, Baek HL, Lee MS, Park DI*
- 3538 Continuing episodes of pain in recurrent acute pancreatitis: Prospective follow up on a standardised protocol with drugs and pancreatic endotherapy  
*Pai CG, Kamath MG, Shetty MV, Kurien A*
- 3546 Nissen fundoplication vs proton pump inhibitors for laryngopharyngeal reflux based on pH-monitoring and symptom-scale  
*Zhang C, Hu ZW, Yan C, Wu Q, Wu JM, Du X, Liu DG, Luo T, Li F, Wang ZG*

**3556** Diagnosis of eosinophilic gastroenteritis is easily missed

*Abassa KK, Lin XY, Xuan JY, Zhou HX, Guo YW*

**CASE REPORT**

**3565** Fecal microbiota transplantation cured epilepsy in a case with Crohn's disease: The first report

*He Z, Cui BT, Zhang T, Li P, Long CY, Ji GZ, Zhang FM*

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## Cautiously using natural medicine to treat liver problems

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### Abstract

Natural medicine is a system of therapy that administrates natural agents and their derivatives to treat human diseases. This medicine has been used to treat many kinds of human diseases for thousands of years. The treatment protocols of natural medicine

are integrative in nature, and are required to utilize the most appropriate therapies to address the needs of the individual patient. Because of the relative convenience, safety and efficacy, natural medicine is now increasing worldwide. Naturopathic doctors are licensed in many areas of the world and regulated partly by law in these areas, which is quite different from various other forms of complementary and alternative medicine. Liver diseases, such as hepatitis, liver cirrhosis and liver carcinoma, are serious health problems worldwide. Nearly half of the natural agents used in treatment of liver diseases today are natural products and their derivatives. Although natural medicine is beneficial and safe, physicians should pay close attention to the potential side-effects of the naturopathic agents, which lead to liver injury, interstitial pneumonia and acute respiratory failure. Therefore, when administrating naturopathic protocols to patients for the treatment of liver diseases, we should try our best to prevent and avoid as much as possible the negative impact of these medicines. This article highlights the current practice and recommended improvement of natural medicines in the treatment of liver diseases and gives some specific examples to emphasize the prevention and management of adverse reactions of the natural agents and suggests that natural medicine should be cautiously used to treat liver problems.

**Key words:** Caution; Natural medicine; Herb; Natural nutraceutical; Liver disease; Adverse reactions

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**Core tip:** We discuss recent experiences in administrating natural medicines to treat liver problems, and the adverse reactions of some natural medicines. Natural medicines provide benefits to patients with liver diseases, such as hepatitis, liver cirrhosis and liver cancer. Close attention should be paid to the prevention of side effects of the natural medicines, however, when liver diseases are treated to avoid as far as possible the negative impact of these medicines.

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## INTRODUCTION

Natural medicine is a system of therapy in which the practice of medicine relies on natural agents and their derivatives to treat human diseases<sup>[1,2]</sup>. It is also defined as a practice of diagnosis and prevention of human sickness<sup>[3]</sup>. This medicine has been used for thousands of years in the treatment of many kinds of human diseases<sup>[4-6]</sup>. Natural medicine contains many complementary and alternative methods in the prevention and treatment of diseases<sup>[7]</sup>. Agents used in naturopathy must exist in nature, with no chemical additives, and have undergone no or very little processing, such as herbs, nutrients, diet supplements, etc. Both naive healthcare workers and the general public appreciate the use of natural medication<sup>[8]</sup>. Unlike various other forms of complementary and alternative medicine, natural medicine is regulated in part by law. And, naturopathic doctors are now licensed in many regions of the North American continent. They have offered patient-centered care, more accessibly discounted care and more time for consulting, and more and more patients prefer to seek healthcare from them<sup>[7,8]</sup>. Nutraceuticals are used as one of the naturopathic approaches to treat human diseases.

The liver is the largest internal digestive organ of our body, which is indispensable in many essential physiologic processes and vulnerable to be impaired by a wide variety of factors, such as toxins, microorganisms, metabolic products, circulatory materials and neoformations<sup>[9]</sup>. There are many types of liver diseases that result from different causes, such as viral hepatitis, alcohol abuse and non-alcoholic fatty liver disease<sup>[10]</sup>. Recent research on functional foods such as nutraceuticals showed that many natural agents exert protective and therapeutic effects on the liver, and some of the other herbal and nutritional supplements also have mechanisms of action that make them beneficial to the liver<sup>[11]</sup>.

Naturopathy is now increasing worldwide and gives merit to the diseased liver in a natural manner, showing effective and curative action for several liver diseases<sup>[2,3,7,12]</sup>. Knowledge about correct eating and lifestyle can be integrated into the everyday practice of managing liver problems<sup>[11,13]</sup>. The aim of natural medicine is to treat the cause of a disease rather than just the symptoms, like allopathic medicine often does. Naturopathy also utilizes evidence-based medicine and modern scientific research to combine conventional and complementary and alternative medicine to treat

the diseases. Naturopathy follows some principles which underlie and are determined by its practice, such as relying on the healing power of nature, finding the root causes of diseases, treating the whole person, personalization, prevention, intent to do no harm, and the doctor serving as teacher for patient education<sup>[3,14]</sup>. Most important of all, these medicines should be given only by physicians (*i.e.*, naturopathic doctors) who are licensed and certified, and who keep in mind good medical ethics and a sense of responsibility. If these rules are not followed, even those natural agents which are claimed to have hepatoprotective effects can also cause serious adverse drug reactions.

This article is essentially about natural medications, natural herbal medicines, food and natural nutraceuticals rather than prescribed medications of the liver, and highlights the current practice and recommended improvement of some natural medicines in the treatment of liver diseases; it also discusses the side effects of natural agents for liver disease and suggests that we should pay close attention to such and apply them cautiously.

## HERBS FOR TREATMENT OF LIVER DISEASES

In both ancient western medicine and traditional oriental medicine, herbs have been used for centuries for the treatment of liver diseases<sup>[4,6,9]</sup>. In the western world, Avicenna, who was one of the most famous physicians of the old era, authored *The Canon of Medicine*. In the Canon, Avicenna introduced many hepatoprotective plants and compound drugs, and some formulas that have the effect of treatment of liver diseases<sup>[9]</sup>.

Chinese herbal medicine is based on clinical experience and practice, and has been established over thousands of years<sup>[4]</sup>. The formation of prescriptions with combination herbal formulas has experienced a long history. In a formula, the selection of individual herbs must be strictly guided by the theory of traditional Chinese medicine, and must highlight the overall concept of personalized treatment<sup>[15]</sup>. Now, the efficacy and safety of a number of herbal products in the treatment of liver diseases have been demonstrated by correlated clinical studies<sup>[9]</sup>.

## HERBAL FORMULAS FOR LIVER DISEASES

Sho-saiko-to, also known as Xiao-Chai-Hu-Tang and Minor Bupleurum Formula in Chinese, is commonly used to treat chronic hepatitis and is also effective for liver cirrhosis. This herbal medicine also has the effect of preventing development of hepatocellular carcinoma<sup>[4,15]</sup>. It is the first herbal drug approved by the Food and Drug Administration (FDA)<sup>[5]</sup>. Approximately

**Table 1** Information about typical natural herbal formula "Sho-saiko-to" for treatment of liver diseases

Natural medicine	Ref.	Literature type	Effects and mechanisms/possible mechanisms	Adverse reactions
Sho-saiko-to	Shimizu <sup>[4]</sup> , 2000	Review	Preventive and therapeutic effects on experimental hepatic fibrosis; inhibition of oxidative stress in hepatocytes and hepatic stellate cells	Not mentioned
	Yamashiki <i>et al</i> <sup>[5]</sup> , 1992	Article	Efficacious against chronic liver diseases, malignant diseases and acute infectious diseases	Not mentioned
	Yamashiki <i>et al</i> <sup>[6]</sup> , 1999	Article	Suppressing liver cancer development; increasing interleukin-12 production and macrobiotic activity in liver cirrhosis patients	Not mentioned
	Lee <i>et al</i> <sup>[15]</sup> , 2011	Review	1 Protecting against development of hepatocellular carcinoma in cirrhotic patients 2 Reducing hepatocyte necrosis and enhancing liver function 3 Inhibiting hepatic fibrosis by reducing activation of stellate cells 4 Inhibiting hepatic lipid peroxidation, promoting matrix degradation, and suppressing extracellular matrix accumulation	Interstitial pneumonia and acute respiratory failure

**Figure 1** Leaves and blooming flower of silymarin.

1500 years ago, this herbal drug was introduced into Japan from China as an oriental classical medicine, and it used to be the most representative agent in Kampo medicine (traditional Japanese medicine). Here the word "Kampo" stands for "Han method", coming from a culture source in the Han era (from 206 before Christ to 220 Anno Domini) of China<sup>[16]</sup>.

Various clinical trials have shown that this herb drug can protect against the development of hepatocellular carcinoma in patients with cirrhosis, and some basic science studies have demonstrated that it also could enhance liver function and reduce hepatocyte necrosis. Although the therapeutic efficacy of Sho-saiko-to has been well studied and the formula is widely used in the treatment of liver diseases, the mechanism by which the formula protects hepatocytes against hepatic fibrosis and carcinoma remains unclear<sup>[15]</sup>. In 1994, on the basis of large amount of studies, the Ministry of Health and Welfare of Japan approved the use of this Kampo in enhancing liver health and listed it in Japanese national formulary<sup>[5,16]</sup>. Since then, Sho-saiko-to has become a widely used ethical drug in the treatment of hepatitis and liver cirrhosis in Japan<sup>[6,16]</sup>.

At one time, in this country, Sho-saiko-to had been widely prescribed to patients with all types of hepatitis

for long-term treatment<sup>[15]</sup>. This led to the spectacular scenario that over 1.5 million hepatitis patients consumed this traditional Chinese herbal formula in Japan<sup>[6,16]</sup>. Unfortunately, the long-term consumption of Sho-saiko-to, resulted in some severe adverse effects, such as interstitial pneumonia and acute respiratory failure. In March 1996, the media disclosed that in the past 2 years after this Kampo was approved in Japan, 88 hepatitis patients developed interstitial pneumonitis, including 10 deaths resulting from acute respiratory failure, due to taking of this drug<sup>[15]</sup>. Information was urgently put out by the Japanese authorities, and the situation became known as the "Sho-saiko-to Event"<sup>[17]</sup> (Table 1).

## HERBAL MEDICINES FOR LIVER DISEASES

There are several herbal plants worth describing because they have significant effects of hepatoprotection as well as therapeutic activities (Table 2).

### Silymarin

Silymarin (*Silybum marianum*), also called the milk thistle plant (Figure 1), is native to Asia and Southern Europe<sup>[18,19]</sup>. The uses of *Silybum marianum* as a hepatoprotective agent to treat different types of liver and biliary disorders in European countries can be dated back to 2000 years ago<sup>[11,18-20]</sup>. The oldest reported use of milk thistle was from the ancient Greeks and Romans, who used this plant as a treatment for liver ailments and snake bites. Then, during the Middle Ages, milk thistle was recommended to treat liver toxicity. Now, the German Commission E, the German governmental equivalent of the FDA, recommends it for treatment of toxin-induced liver problems and liver cirrhosis, and as a supportive treatment for chronic diseases of the liver<sup>[19]</sup>.

Although milk thistle has a considerably long history in the treatment of liver diseases, it was not

**Table 2** Information of some natural herbal medicines for treatment of liver diseases

Natural medicines	Ref.	Literature type	Effects and mechanisms/possible mechanisms	Adverse reactions
Silymarin	Bahmani <i>et al</i> <sup>[18]</sup> , 2015	Review	Antioxidant; anti-inflammatory; cell permeability regulator and membrane stabilizer; stimulating liver regeneration and inhibiting deposition of collagen fibers	Mild gastrointestinal disorders
	Zhu <i>et al</i> <sup>[21]</sup> , 2016	Review	Anticancer by regulating cancer cells growth, proliferation, apoptosis, angiogenesis, such as hepatocellular carcinoma; antioxidant, immunomodulatory, anti-fibrotic, anti-proliferative, and antiviral activities	Not mentioned
	Csupor <i>et al</i> <sup>[22]</sup> , 2016	Review	Stimulating liver regeneration; antioxidant, anti-inflammatory and hepatoprotective; treatment of mushroom poisoning, hepatitis, cirrhosis and fibrosis of liver	Mild gastrointestinal and allergic reactions
Long pepper	Kumar <i>et al</i> <sup>[23]</sup> , 2011	Review	Hepatoprotective activity; treatment for chronic bronchitis, asthma, constipation, gonorrhoea, paralysis of tongue, diarrhea, cholera, chronic malaria, viral hepatitis, stomachache, spleen diseases, cough, and tumors	Contraceptive activity; should be avoided during pregnancy and lactation
	Mansour <i>et al</i> <sup>[24]</sup> , 2009	Article	Increasing activity of transglutaminase; enhancing antioxidant activities in fibrotic liver; anti-tussive, anti-asthmatic, anti-allergic, antitubercular, antipyretic, hypotensive, hypoglycemic, anthelmintic and coronary vasodilatory	Not mentioned
Holy Basil	Jiang <i>et al</i> <sup>[25]</sup> , 2013	Review	Anti-hepatitis B virus activity <i>in vitro</i>	Not mentioned
	Lahon <i>et al</i> <sup>[26]</sup> , 2011	Article	Hepatoprotective activity and synergistic with silymarin; anti-inflammatory activity	Not mentioned
	Baliga <i>et al</i> <sup>[27]</sup> , 2013	Review	Anti-inflammatory, analgesic, antipyretic, antidiabetic, hepatoprotective, hypolipidemic, antistress, and immunomodulatory activities	Not mentioned but being considered non-toxic
	Singh <i>et al</i> <sup>[28]</sup> , 2007	Review	Anti-inflammatory, antipyretic, hypotensive, anticoagulant and immunomodulatory activities; chemopreventive and hypolipidemic activities	Not mentioned
	Prakash <i>et al</i> <sup>[30]</sup> , 2005	Review	Antifertility, anti-cancer, anti-diabetic, antifungal, antimicrobial, hepatoprotective, cardioprotective, antiemetic, antispasmodic, analgesic, adaptogenic and diaphoretic actions	Not mentioned

**Figure 2** Fruits of long pepper.

until 1968 that silymarin (the medicinal ingredient of milk thistle) was found in milk thistle seed extract. Silymarin is a complex mixture of flavonolignans, including silybin, isosilybin, silychristin, silydianin, and taxifolin. It has been shown that its hepatoprotective effects are mainly contributed by its free radical scavenging property and antioxidant activity<sup>[19]</sup>. Although its mechanisms of action are not yet fully understood, the hepatoprotective activity of silymarin has been shown to act in different ways, such as through antioxidant and anti-inflammatory activities, regulation of permeability of the cell wall, stabilization of cellular membranes, stimulation of liver regeneration

and anti-fibrotic, immunomodulatory, antiviral and anti-cancer activities<sup>[18,21]</sup>. It is also used as a dietary supplement for food remedy, as the leaves of this plant have been used in salads and traditionally the fruit has been roasted as a coffee substitute<sup>[18,19]</sup>. The preparations of milk thistle are safe, well tolerated, and few adverse side effects have been reported, except allergic reactions and mild gastrointestinal symptoms. Long-term use of this herb is considered to be safe and no incidence of significant abnormality has been reported<sup>[18,19,22]</sup>.

### Long pepper

Long pepper (*Fructus Piperis Longi*; Figure 2) is another herb commonly used in Chinese medicine, and also has been used in the Ayurvedic system of medicine. This plant is low in cost, easy-to-obtain, and effective for various diseases, such as hepatotoxicity, inflammation, diabetes, obesity, depression and cancer<sup>[23]</sup>. It has been demonstrated as capable of modulating liver function by enhancing antioxidant activities.

A study has shown that the extract of *Fructus Piperis Longi* treats liver diseases by reducing the activities of transglutaminase, such as serum aspartate amino transaminase, alanine aminotransferase, alkaline phosphatase and gamma-glutamyltransferase, which are the main causes of the development of liver cirrhosis, and also by reducing bilirubin (total, direct



Figure 3 Holy basil as green vegetable.

and indirect) content, which leads to jaundice<sup>[24]</sup>. The ethanol extract of long pepper was found to possess superior activity against hepatitis B virus *in vitro*<sup>[25]</sup>. In rodents, this plant was assessed for its hepatoprotective effect against CCl<sub>4</sub>-induced acute, chronic reversible and irreversible liver damage.

Furthermore, as a spice used in cooking, the plant is free from adverse effects, as no deaths have been reported with the use of high doses of the plant extracts. However, some studies reported that the plant had exerted contraceptive activity in experimental models; hence, use of this plant should be avoided during pregnancy and lactation<sup>[23]</sup>.

### Holy basil

*Ocimum sanctum* L. (Labiatae; popularly known as "Tulsi" in Hindi and "Holy Basil" in English) is known as an herb which is an important hepatoprotective plant in various traditional and folk systems of medicine, including traditional Chinese medicine, Ayurveda, Greek, Roman, Siddha, and Unani. It is also commonly used as a green vegetable (Figure 3) in a delicious Thai cuisine, a stir-fry with rice, seafood or meat<sup>[26-29]</sup>. This plant contains many important phytochemicals that present various activities of analgesia, anti-diabetes, anti-inflammation, antipyresis, antistress, hepatoprotection, hypolipidemia, immunomodulation and anti-neoplasia<sup>[27,29,30]</sup>. For the treatment of liver diseases, some studies have shown that the combination use of holy basil and silymarin demonstrated synergistic hepatoprotective activity<sup>[26]</sup>. No significant side effects of this plant have been reported, and it is considered non-toxic to humans and could be used as a chemopreventive and radioprotective agent<sup>[27]</sup>.

## FOOD AND NUTRITIONAL SUPPLEMENTS FOR LIVER DISEASES

Several natural foods and drinks with nutritional supplements have been shown to be both safe and effective in the therapy of liver diseases<sup>[10,11]</sup>. Natural foods, especially plant-based foods, have many advantages in

promoting liver health<sup>[10,31]</sup>. So, traditionally, they have been usually used in the treatment and prevention of liver diseases throughout the world<sup>[26]</sup>. The mechanisms of hepatoprotective effects in naturopathic medicine include anti-oxidative activity, inhibition of hepatic stellate cell activation, activation of physiological defense, and suppression of hepatocarcinogenesis by cell cycle arrest and induction of apoptosis<sup>[4,32]</sup>. Natural foods in our everyday life also could be beneficial for patients with liver disease (Table 3).

### Coffee

Coffee is the most popular beverage in the world and is a rich source of dietary antioxidants. Several epidemiological and case-controlled studies showed that coffee drinking is associated with better results of serum liver function tests and with a reduced risk of cirrhosis and hepatocellular carcinoma. The mechanisms involved are related to the anti-fibrosis, anti-carcinogenesis, and antioxidant effect of the drink. Coffee intake more than 2 cups per day protects against progression of almost all forms of liver diseases<sup>[10,33]</sup>. However, there is no direct evidence that increasing the consumption of a coffee drinker will be beneficial or starting to drink coffee for an abstainer from coffee will improve their liver disease. And, caffeine is a psychoactive drug, increasing alertness and cognition; so, coffee drinkers have some common features of drug abuse, such as clinical dependency, withdrawal, tolerance or intoxication<sup>[10]</sup>.

### Fruits

Popular plant foods, such as apple and citrus, also have been shown to have beneficial effects against a number of chronic diseases. Apple and mandarin are also rich in antioxidants. An animal study confirmed that a diet made of dried apple and mandarin orange is protective against liver impairment induced by tamoxifen in rats<sup>[34]</sup>. Another study revealed the hepatoprotective efficacy of apple pomace aqueous extract, as it had inhibited CCl<sub>4</sub>-induced hepatocyte apoptosis<sup>[35]</sup>. However, fruit allergy which represents one of the most common allergenic responses, is hard to avoid. When some patients eat a particular fruit (apple, citrus, peach, *etc.*), oral allergy syndrome may be evoked<sup>[36]</sup>.

### Plant phytoalexin

Natural resveratrol is a plant phytoalexin that is produced by plants in response to damage, and is found in many plants, such as mulberries, red grapes, peanuts, soy, knotweed, and sickle pod<sup>[37,38]</sup>. Resveratrol has been shown to improve lipid metabolism, prevent expression of liver inflammatory markers and protect against nonalcoholic fatty liver disease. Furthermore, it activates sirtuins, which could extend lifespan in many organisms<sup>[39]</sup>.

Vegetables, especially green leafy vegetables, can be taken as measures against the lack of dependable hepatoprotective drugs in modern allopathic medicine to treat and prevent liver damage<sup>[26,40]</sup>. Many other

**Table 3** Information of some natural plants for treatment of liver problems

Natural plants	Ref.	Literature type	Effects and mechanisms/possible mechanisms	Adverse reactions
Coffee	Masterton <i>et al</i> <sup>[10]</sup> , 2010	Review	Potential to reduce risk of abnormal liver function tests, cirrhosis and hepatocellular carcinoma	Clinical dependency, withdrawal, tolerance or intoxication
	Wadhawan <i>et al</i> <sup>[33]</sup> , 2016	Review	Reducing incidence of fibrosis and cirrhosis, hepatocellular carcinoma rates, and decreasing mortality	Not mentioned
Apple	Codoñer-Franch <i>et al</i> <sup>[34]</sup> , 2013	Article	Protective action against oxidative stress induced by tamoxifen in rats	Not mentioned
	Sharma <i>et al</i> <sup>[35]</sup> , 2016	Article	Antioxidant activity; able to induce protein expression of nuclear factor (erythroid-derived 2)-like 2 to inhibit CCL <sub>2</sub> -induced apoptosis	Not mentioned
Resveratrol	Burns <i>et al</i> <sup>[38]</sup> , 2002	Review	anti-oxidative, anti-carcinogenic, and antitumor properties	Not mentioned
	Andrade <i>et al</i> <sup>[39]</sup> , 2014	Article	Improving lipid metabolism, decreasing incidence of nonalcoholic fatty liver disease, pro-inflammatory profile in liver of mice fed with obesity-inducible diets	Not mentioned

natural foods and nutritional supplements contain natural compounds that are beneficial to liver health, such as bioflavonoids, carotenoids, crude plant extracts, polyphenols, terpenoids, sulphoraphane, and vitamins<sup>[37]</sup>. A number of different natural agents protect against liver diseases, as well<sup>[26]</sup>. There is a long list of these agents, including quercetin, genistein, catechins, curcumin, and rosemary essential oil<sup>[41]</sup>.

## DISCUSSION

The natural formula has a diversity of therapeutical activities coming from multiple active elements<sup>[1]</sup>. This diversity is the most suitable treatment for the heterogeneity of liver cancer cells, which causes in most circumstances the treatment failure in modern allopathic medicine<sup>[42]</sup>. A naturopathic formula often contains several active elements that protect against liver diseases, such as antioxidant, anti-inflammatory, antiviral and anti-cancer elements<sup>[15]</sup>. The mechanisms of anti-cancer properties are closely associated with the activity of pro-apoptosis, inhibition of proliferation, and cell cycle arrest that are presented by these active elements<sup>[4,27]</sup>.

Naturopathy is regulated in part by law, which is quite different from various other forms of complementary and alternative medicine<sup>[7]</sup>. The scientific debate on natural medication and its integration with the conventional or mainstream medicine has continued for many years in western society<sup>[43]</sup>. Safety of natural medication is concerned with treatment of liver problems<sup>[44,45]</sup>. A formula composed of two or more drugs has been demonstrated as more beneficial for disease treatment, but the selection of individual herbs in the formula must be strictly guided by the principles underlying Chinese herbal medicine.

Had the fundamental essence of traditional Chinese medicine been followed, the "Sho-saiko-to Event" in Japan would have been avoided<sup>[4,15]</sup>. The event was not an accident, but the inevitable result of western medicine physicians administering Chinese medicine without applying the underlying principles of traditional

Chinese medicine theory in Japan. Some experts suggest that under the theory and method of modern western medicine pharmacology, the mechanism and the curative effect of traditional Chinese medicine are often difficult to illustrate.

Based on traditional Chinese medicine theory, it is inappropriate to apply the Sho-saiko-to decoction to all patients with liver disease, and the drug also should not be administered to all the patients without change. This herbal medicine has been used to treat pyretic diseases in China for around 3000 years. However, there are no reports on large-scale pulmonary side effects as occurred in China<sup>[4,5]</sup>. The essence underscores that diagnosis and treatment must be based on an overall analysis of the illness and the patient's personalized condition. Long-term high-dose administration of the decoction is fatal, and it is difficult to believe that one of the patients had been taking this formula continuously for 3 years with a total of 7.5 kg of the drug<sup>[16]</sup>.

Many factors may affect the efficacy of drugs and even enhance the side effects. For Sho-saiko-to, it is reported that higher risk of adverse reactions is related to elderly age, co-administration of interferon and most importantly the duration of medication<sup>[15]</sup>. Even acute hepatitis was reported after long-term continual consumption of this decoction, which reminds us that even some herbs which are claimed to have hepatoprotective effects could probably lead to an adverse drug reaction<sup>[46]</sup>. Although the therapeutic effect of herbs is beneficial, side effects must be treated with the greatest possible care.

Besides the time duration and amount of consumption, dynamic modification of this Kampo formula is necessary<sup>[47]</sup>. Serious adverse effects can be prevented when the strong ginseng is replaced by the gentler dangsen (*Codonopsis pilosula*)<sup>[48]</sup>. Banxia (*Rhizoma pinelliae*), another herb in the formula, is poisonous to the gastrointestinal tract and inhibitory for the respiratory center and peripheral nerves<sup>[49]</sup>. In routine traditional Chinese medicine practice, when the patient has the symptom of cough, ginseng, jujube and fresh ginger must be removed from the formula

and the fruit of Chinese magnoliavine and dried ginger are used instead; moreover, pollen is employed instead of banxia if the patient has the symptom of thirst<sup>[50,51]</sup>. Therefore, personalized modification of each herb in the Sho-saiko-to formula is of paramount importance<sup>[52]</sup>.

## CONCLUSION

Natural medicine is a holistic approach to treat liver diseases. Naturopathy for liver disease is developing rapidly in clinical practice and theoretical research. However, the mechanisms of function and safety remain incomprehensive and even controversial. Natural agents have multiple therapeutic effects, based upon their antioxidant, anti-inflammatory, antiviral and antitoxic properties, etc. Because of the diverse therapeutical effects and relatively mild side effects, patients usually appreciate the use of natural agents to treat liver diseases. And for the sake of patients' safety, it is appropriate to try natural medication before allopathic medicine in the treatment of liver problems.

Although the therapeutic effect of natural medication is beneficial, side effects must be treated with the greatest possible care. The best way to prevent the complications is to ensure that these medicines be given only by physicians who are licensed and certified. And, good medical ethics and sense of responsibility are also absolutely necessary for the naturopathic doctors. Naturopathic doctors must follow the principles which underlie and are determined by the practice of natural medicine. For patients, it is necessary to follow the guidance of the doctor when natural drugs are used in the treatment of liver diseases.

There are safety problems that still require further study. On the one hand, natural medicines are often mistaken as agents with no side effects and the cheap prices make them easy to get and use. On the other hand, there exists a lack of regulators to oversee the use of natural medicine. These are the main issues that lead to long-term and large amount of consumption of natural drugs and bring about adverse reactions. Both the doctor and the patient should be aware of the potential risks of drugs and be cautious when using them. Each drug has certain indications, specific usage and dosage. An overdose more than the maximum dosage will certainly lead to some adverse reactions. Even the so-called natural medicines or the common foods cannot be abused to treat diseases.

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