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Beneficial effects of Chinese herbs in the treatment of fatty liver diseases

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ABSTRACT

Eating habits and lifestyle directly impact general health. Consumption of fat- and sugar-rich foods and alcohol increase the risk of developing fatty liver disease. The prevalence of fatty liver disease is markedly critical, and its pathogenesis and progression are complicated. Chinese herbal medicine has been used to treat and prevent human diseases through-out history, and is a rich source of biologically active substances with unique curative properties. More recently, Chinese herbs and their extracts have been identified as a novel source of potential therapeutic agents in the prevention and treatment of fatty liver disease. Beneficial effects of these herbal medicines mean that they can be classified as novel candidates for the treatment and prevention of both alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD), in place of conventional allopathic treatments. In this review, we explore the current literature related to herbal medicines used for the treatment of or protection against fatty liver diseases and describe their mechanisms of action.

1. Introduction

Eating habits and lifestyle directly impact human health and disease pathogenesis. Chronic diseases, including fatty liver disease, are a common problem for people worldwide. Fatty liver disease can be caused by many factors, including the frequent consumption of high-calorie foods or alcohol, and the development of other chronic diseases. Fatty liver is the initiating state for the development of steatohepatitis (NASH), cirrhosis, and eventually hepatocellular carcinoma.[1,2] Typically, fatty liver disease presents as asymptomatic, and can be divided into two categories: (1) alcoholic fatty liver disease (AFLD): hepatic fat builds up as a result of high alcohol intake, and (2) non-alcoholic fatty liver disease (NAFLD): fat accumulation in the liver is not related to alcohol consumption.[3] Usually, both AFLD and NAFLD do not cause serious problems, and the conditions can be reversed by changes in eating habits or, in severe cases, clinical intervention. However, both conditions may lead to more serious liver diseases including cirrhosis and hepatocellular carcinoma.[4]

Numerous Chinese herbs have been shown to exert a medicinal effect on fatty liver disease as well as preventing the accumulation of fat in the liver in the first place. As in all conditions prevention is better than cure, which means that if fatty liver disease can be prevented by the use of hepatoprotective herbs or diet it may help to reduce the burden of this chronic disease on the global health care system. In this review, we explore the current literature pertaining to the prevalence of fatty liver disease, the effect of diet on its development and its risk factors and pathogenesis, as well as reviewing the Chinese herbs that exhibit hepatoprotective effects against AFLD and NAFLD.

2. Prevalence of fatty liver disease

The prevalence of AFLD and NAFLD are different. In 2016, the

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Abbreviations

ACC	acetyl coenzyme A carboxylase
AFLD	alcoholic fatty liver disease
ALT	alanine transaminase
AST	aspartate transaminase
CAT	catalase
ChREBP	carbohydrate-responsive element-binding protein
CPT-1	mitochondrial carnitine palmitoyltransferase-1
CYP2E1	microsomal protein cytochrome P4502E1
FAS	fatty acid synthase
FFA	free fatty acids
GSH	glutathione
GPx	glutathione peroxidase
GRd	glutathione reductase
HMGCR	3-hydroxy-3-methyl-glutaryl-CoA reductase
IL-1β	interleukin-1β
IL-6	interleukin-6
LPS	lipopolysaccharides
NAFLD	non-alcoholic fatty liver disease
NASH	nonalcoholic sateatohepatitis
Nrf2	nuclear factor erythroid 2-related factor 2
PPAR-α	peroxisome proliferator-activated receptor-α
RNS	reactive nitrogen species
ROS	reactive oxygen species
SREBP-1	sterol regulatory element-binding protein-1
SOD	superoxide dismutase
TC	total cholesterol
TG	total triglyceride
TNF-α	tumor necrosis factor α
WHO	World Health Organization

global prevalence of NAFLD was approximately 25%. The Middle East was found to have the highest NAFLD prevalence (31.8%), followed by South America (30.5%) and Asia (27.4%), respectively. The lowest NAFLD prevalence was observed in Africa (13.5%) (Fig. 1A).[5] The global prevalence of NAFLD is increasing proportionately with obesity and type 2 diabetes mellitus.[6] The prevalence of alcohol associated fatty liver disease is very different from NAFLD. The World Health Organization (WHO) reported that the estimate average global alcohol consumption figure is around 6.4 L of alcohol per person and around three million deaths occur annually as a result of the harmful use of alcohol, which accounts for 5.3% of all global deaths. Moreover, alcohol intake can result in more than 200 diseases and injuries, including AFLD.[7] In the USA, the AFLD prevalence rate was estimated to be 4.3% between 2001 and 2002 and remained stable at 4.7% in 2015–2016. In addition, in patients with stage II or higher AFLD fibrosis increased by 2-fold (Fig. 1B).[8] In some regions of China, the prevalence of fatty liver disease was 5.32%, and was significantly higher in males than females, with this figure rising to 10% in alcohol users.[9] NAFLD prevalence was higher than AFLD but NAFLD prevalence experienced incremental increases with alcohol consumption.

3. Effect of diet and other risk factors in the development of fatty liver disease

Fig. 1C illustrates the effects of diet and other risk factors for fatty liver disease. The phrase “You are what you eat” reminds us that our eating habits influence our health.[10] Western diets are associated with obesity and NAFLD,[11,12] hypercaloric diets high in fats, sugars, or both, increase hepatic fat content.[13] Soft drinks and desserts containing a large amount of sugar, including fructose, are central to these eating habits and are major contributors to diet induced NAFLD.[14,15] Moderate alcohol intake can reduce the risk of cardiovascular disease,[16,17] however, excessive alcohol intake can result in AFLD which may develop into hepatosteatosis, cirrhosis, and hepatocellular carcinoma.[18–21] Some foods may contain microbial toxins including aflatoxin, produced by mold, which can accumulate and damage the liver.[22,23] Dietary nutrients are important for human health but they are also essential for the gut microbiota that reside in our intestines.[24] Many studies have shown that our diet influences the gut microbiota and their metabolites, and these metabolites subsequently translocate to the liver via the portal vein and may affect liver function, for example, lipopolysaccharides (LPS) can result in hepatic inflammation.[25–28] In fact our diets may not only cause fatty liver disease but may also induce a number of other diseases.[5] Many diseases have been reported as risk factors for the development of fatty liver disease including obesity,[1] type 2 diabetes,[29,30] metabolic syndrome,[31] some genetic conditions,[32,33] viral infections,[34,35] and adverse drug reactions.[36,37] In China, the risk of fatty liver disease is significantly increased for alcoholic patients, as well as in patients with hypertension, diabetes, and coronary heart disease.[9] Understanding the genetic and environmental risk factors for fatty liver disease and their distribution in the global population is crucial in the development of treatment and prevention strategies, the implementation of public health policy and the recognition of this important chronic liver disease.[38]

4. Fatty liver disease pathogenesis

Fatty liver disease is defined as the accumulation of more than 5% fat tissue in the liver.[39] As mentioned in the introduction, fatty liver can be split into two categories, AFLD and NAFLD. Fatty liver disease is not a serious problem but it can result in the development of steatohepatitis (NASH), cirrhosis, and eventually hepatocellular carcinoma.[1,2] Liver diseases comprise a broad spectrum of diseases ranked from asymptomatic fatty liver disease to steatohepatitis to cirrhosis[40,41] (Fig. 2A). The induction of fatty liver usually includes alcohol, high-fat food, or high sugar food intake (Fig. 2B), with each experiencing a different pathogenic mechanism. In this review, we will focus on the pathogenesis of the early stages of fatty liver disease.

4.1. Alcoholic fatty liver disease (AFLD)

The mechanisms of alcohol-induced fatty liver injury are complicated and not completely understood. Typically, alcohol metabolites are degraded by alcohol dehydrogenase (ADH) forming acetaldehyde, which is toxic to the cells. This is then, metabolized to acetate by aldehyde dehydrogenase.[42] Reduction of ADH activity can be caused by alcohol intake.[43] In addition, acetate can be used in fatty acid and cholesterol biosynthesis resulting in the development of a fatty liver.[44] Alcohol promotes the generation of free radicals like reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can lead to mitochondrial dysfunction and subsequently reduce the mitochondrial fat oxidation raising hepatic fat droplet accumulation.[45] ROS and RNS also elevate oxidative stress increasing lipid toxicity that releases the pro-inflammatory cytokines.[46] Alcohol consumption also induces microsomal protein cytochrome P4502E1 (CYP2E1) expression and activates the Kupffer cells generating pro-

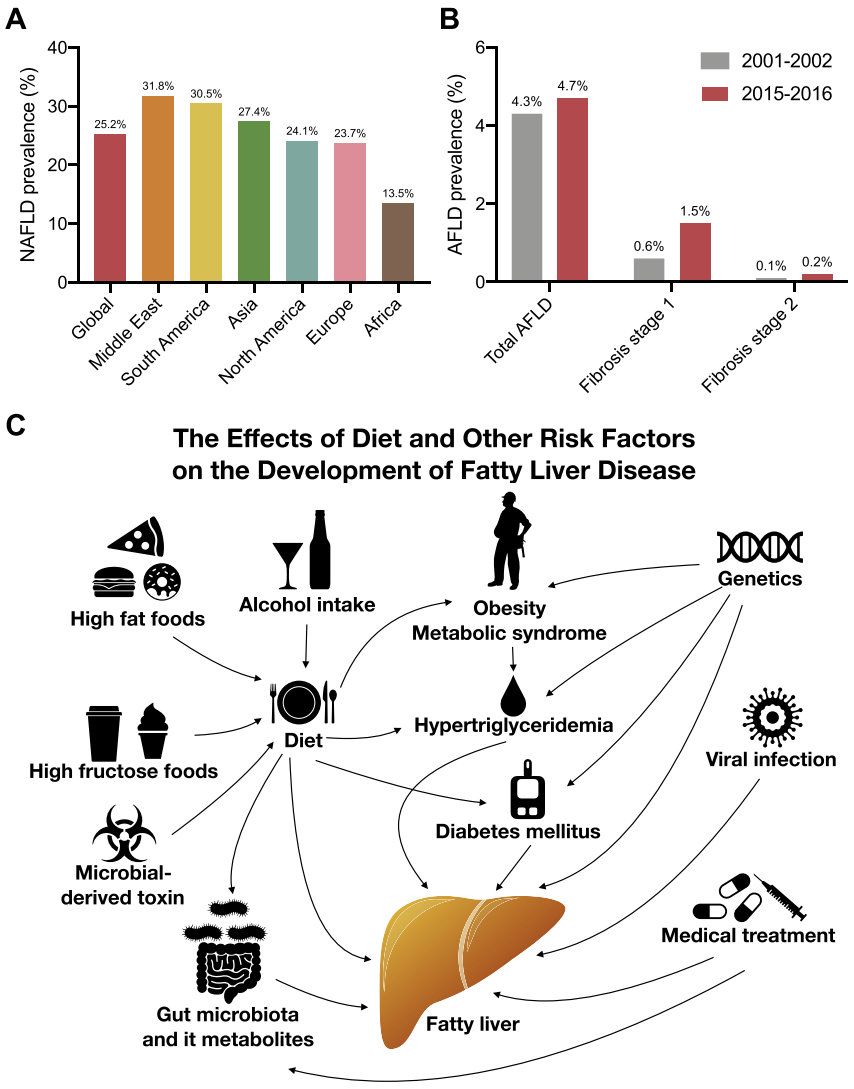

Fig. 1. (A) The prevalence of non-alcoholic fatty liver disease; (B) the prevalence of alcoholic fatty liver disease; and (C) the effects of diet and other risk factors on the development of fatty liver disease.

inflammatory cytokines, proinflammatory tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, which lead to liver inflammation.[44,47,48] The sterol regulatory element-binding protein-1 (SREBP-1) and fatty acid synthase (FAS) are key factors regulating lipid metabolism, and the inhibition of SREBP-1 and FAS has been shown to prevent AFLD.[49,50] Alcohol exposure also activates the peroxisome proliferator-activated receptor- α (PPAR-α), and subsequently accelerates synthesis of various fatty acids, resulting in AFLD.[51] While activation of mitochondrial carnitine palmitoyltransferase-1 (CPT-1) retards the transport of fatty acids into the mitochondria for oxidation.[44] Alcohol intake leads to the dysbiosis of the gut and increases intestinal permeability, resulting in increased translocation of LPS to the liver. Activating the Kupffer cells leading to liver inflammation.[44,52]

4.2. Non-alcoholic fatty liver disease (NAFLD)

NAFLD progression is different from AFLD. In the case of high-fat diets there are several factors at play in the progression of fatty liver disease. However, the mechanisms involved in NAFLD are not fully understood. High-calorie diets can elevate the storage of excessive fat in adipose tissues, causing adipocyte hypertrophy as well as adipose tissue expansion, leading to obesity. Free fatty acids (FFA), from adipose tissues, can be released into the liver stimulating the expression of key factors controlling cholesterol synthesis, including 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR), as well as dysregulating critical fatty acid synthesis factors SREBP1-c, acetyl coenzyme A carboxylase (ACC), and FAS.[53] These enzymes increase the synthesis of liver lipids, like cholesterol and

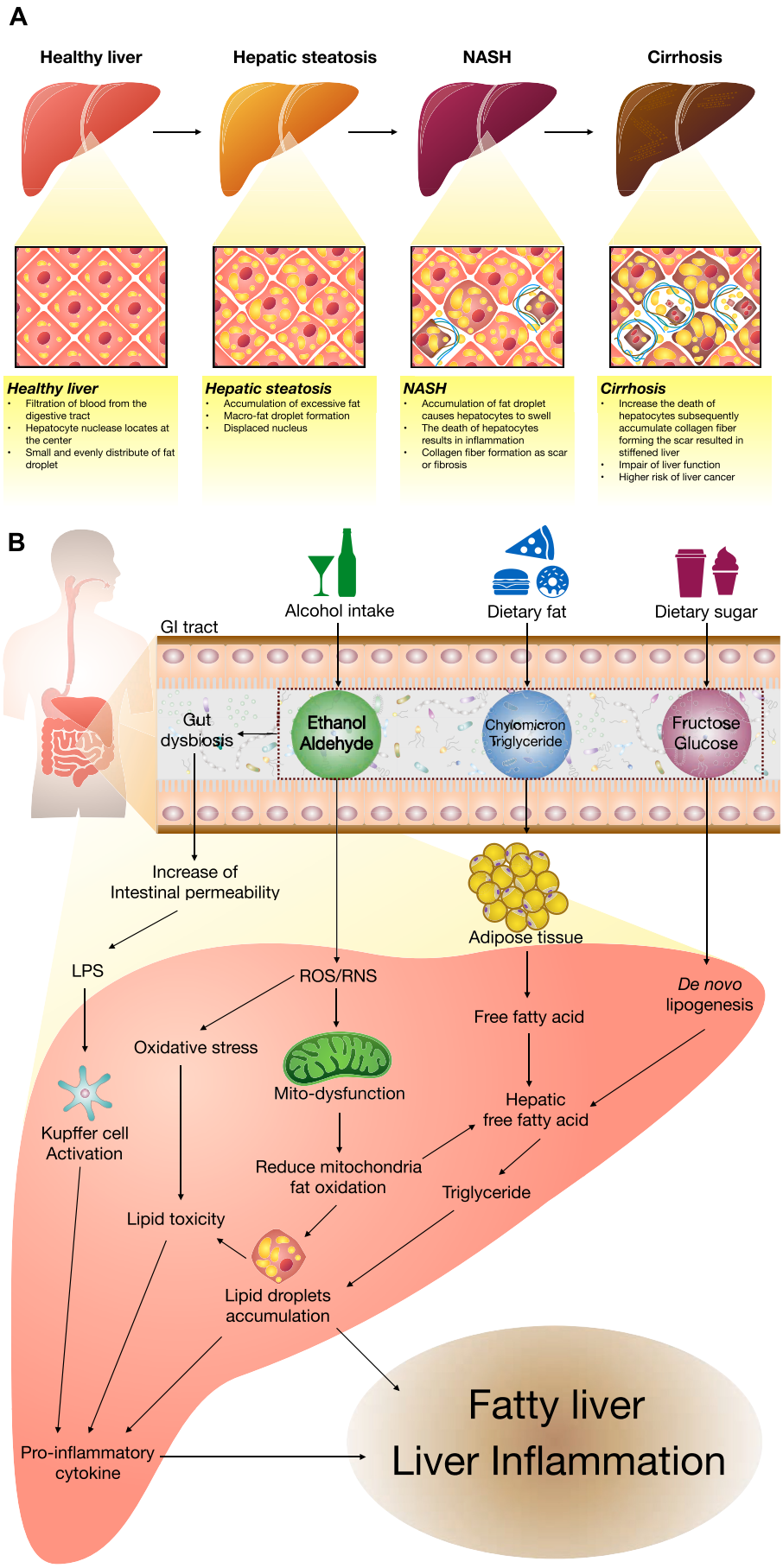

Fig. 2. (A) The spectrum of liver diseases; (B) the pathogenesis of fatty liver disease caused by alcohol intake, dietary fat, and dietary sugar.

triglycerides. While the inhibition of PPAR-α and CPT-1 can result in decreases in fatty acid metabolism and β-oxidation, leading to the development of hepatic steatosis.[53] Similar to in AFLD, CYP2E1 is a regulator of oxidative stress and inflammatory cytokines in NAFLD progression.[54] Gut-derived LPS is also a factor in the pathogenesis of NASH.[28]

A high-fat diet is not the only cause of NAFLD, high-fructose diets have also been shown to result in NAFLD. After fructose intake, it is rapidly absorbed into the bloodstream and liver.[55] The hepatic metabolism of fructose increases *de novo* lipogenesis and inhibits β-oxidation, allowing fat accumulation in the liver.[56] ACC and FAS are important enzymes involved in *de novo* lipogenesis when carbohydrates are metabolized to fatty acids.[57,58] Changes in the carbohydrate-responsive element-binding protein (ChREBP) and SREBP-1 are associated with hepatic lipogenesis induced by fructose intake and the development of NAFLD.[59,60] In addition, CPT-1 which is involved in the metabolism of long-chain fatty acids and β-oxidation is also dysregulated.[61] Fructose consumption is known to alter transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) expression, and this transcription factor is also known to participate in hepatic fatty acid metabolism and the promotion of hepatosteatosis.[62] A recent study has found that the cause of fat accumulation in the liver following fructose consumption is closely associated with fructokinase C, ATP consumption, nucleotide turnover and the production of uric acid.[63] Both high fat and high fructose diets cause hepatic inflammation via an increase in pro-inflammatory cytokines which in turn damages the liver and may result in more serious pathogenesis following prolonged exposure.

5. Chinese herbs and fatty liver disease

Various traditional herbal medicines including traditional Chinese Medicine, Ayurveda, Japanese, and Kampo medicine have been used in the treatment of fatty liver disease.[64] Several animal studies have shown that Chinese herbs can protect against fatty liver disease. In this review, we evaluated studies using three kinds of fatty liver disease animal models: (1) alcohol induced fatty liver disease, (2) high-fat diet induced fatty liver disease, and (3) high fructose diet induced fatty liver disease. These studies demonstrate that Chinese herbs protect against fatty liver disease via different mechanisms based on their animal model (Fig. 3).

5.1. Chinese herbs and AFLD

Various Chinese herbs exhibit a hepatoprotective effect against AFLD. Garlic, ginger, bitter gourd, lychee, ginseng, Korean pine, and Turuarame extracts or their compounds attenuate AFLD by improving AST, ALT, hepatic triglyceride and fat accumulation in the liver (Fig. 3A).[65–71] Allicin, the compound found in fresh garlic blends, improves alcohol dehydrogenase activity in AFLD mice. Most of the Chinese herbs that exhibit an attenuation effect on AFLD act as anti-oxidative or anti-inflammatory agents. Allicin and turuarame ethanol extracts downregulated SREBP-1 expression. Allicin, garlic essential oil, citral, and ginseng oligosaccharides increase glutathione concentrations in the liver, indicating that the oxidative stress response is improved by these compounds. Among these Chinese herbs, only bitter gourd and allicin have been reported to reduce hepatic CYP2E1 protein expression. Allicin, ethanol extracts of bitter gourd, and lychee exhibited anti-inflammatory effects against AFLD. In addition, allicin[72] and lychee have been shown to suppress the LPS-CD14-toll-like receptor 4 pathway, and modulate intestinal microbiota dysbiosis and intestinal barrier dysfunction.[73]

5.2. Chinese herbs and NAFLD

The mechanisms underlying the protective effects of Chinese herbs against NAFLD are quite similar to those described for AFLD with most preventing lipogenesis, oxidative stress, and inflammation. However, there are some variations in the pathways used by these Chinese herbs to reduce lipogenesis in NAFLD. Fig. 3B illustrates the Chinese herbs and their anti-NAFLD effect in high-fat diet-induced NAFLD.[74–80] Garlic, ginger and green tea improve blood glucose and insulin levels, while garlic essential oil, with a high proportion of diallyl disulfide, and ginger (citral) can reduce free fatty acid content in the blood stream reducing translocation to the liver thus reducing NAFLD. Garlic essential oil, diallyl disulfide, ginger, citral, Damask rose flowers ethanol extract, green tea polyphenols, and ginkgolide A reduce the concentration of triglycerides, cholesterol, AST and ALT in the blood stream. All the Chinese herbs in Fig. 3B exhibit hepatoprotective effects against high fat-diet induced NAFLD. Some of the Chinese herbs reduce liver weight, fatty liver score, liver cholesterol, and triglycerides. They prevent lipogenesis by suppressing hepatic lipogenesis through inhibition of SREBP-1, FAS, ACC, and HMGCR, as well as increasing β-fatty acid fat oxidation associated with PPARα and CPT-1 expression. In addition, garlic and ginger improved oxidative function preventing NAFLD by reducing lipid peroxidation, and CYP2E1 expression and improving glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GRd), catalase (CAT), and superoxide dismutase (SOD) activity. Moreover, they reduced hepatic inflammation by reducing TNF-α, interleukin IL-1β, and IL-6 expression.

The anti-NAFLD effects of Chinese herbs in dietary sugar induced-NAFLD are based on decreasing *de novo* lipogenesis, increasing β-oxidation, improving antioxidant activity and suppressing inflammation (Fig. 3C).[81–86] All the Chinese medicines in Fig. 3C reduced blood glucose levels. Sesame, loquat, Ceylon leadwort, and *Antrodia cinnamomea* reduced insulin concentrations in fructose induced NAFLD rodent models while most of the Chinese herbs reduced blood TG, TC, AST, ALT, and fatty liver values. Chinese herbs also inhibited SREBP-1, FAS, ACC, and improved PPAR-α expression. Swertimarin, sesame, and loquat reduced lipid peroxidation and improved liver antioxidative enzyme activity while inhibiting Nrf2 expression. Only swertimarin and plumbagin have been reported to have anti-inflammatory effects reducing TNF- α and IL-6 concentrations.

Many drugs have been developed to treat NAFLD but there are huge challenges that need to be overcome before these drugs can progress to clinical trial.[87] In addition, the differences between Chinese Herb and western allotherapy interventions in AFLD/NAFLD still need to be evaluated. Changing dietary patterns, including shifting to a Mediterranean diet, can reduce fatty liver disease.[88,89] To prevent NAFLD, controlling diet and maintaining an exercise routine is vital. Collectively, the major mechanisms of Chinese herbs in ameliorating fatty liver disease (both AFLD and NAFLD) are the inhibition of lipogenesis, increasing fat oxidation, reducing oxidative stress, and suppressing inflammation in the liver. Thus, the use of Chinese herbs as a supplement is an alternative way to prevent the progression of fatty liver disease and may provide potential agents for the treatment of fatty liver disease in the future.

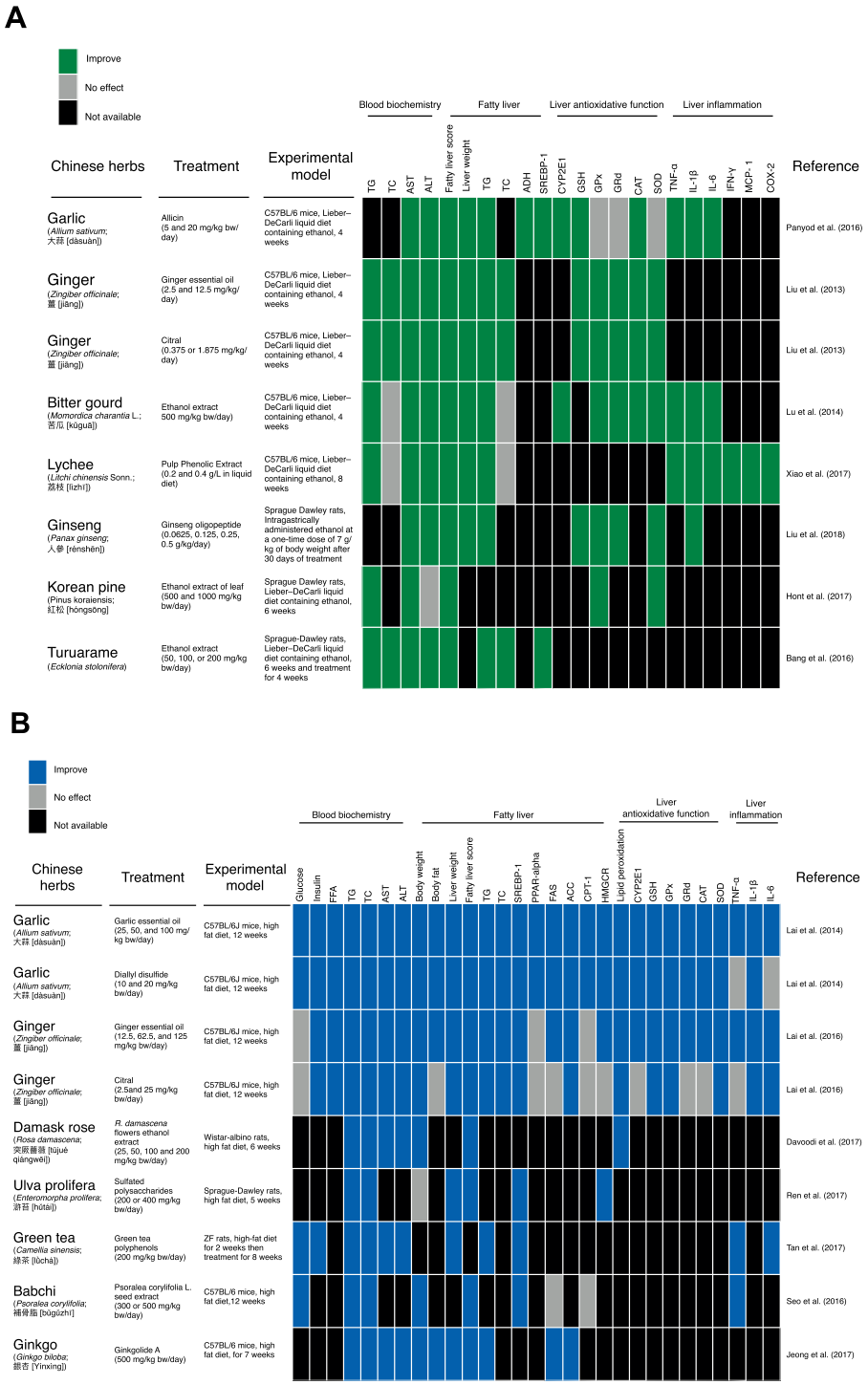

Fig. 3. Chinese herbal medicines shown to protect the liver from (A) alcohol, (B) high-fat diet-, and (C) high fructose-induced fatty liver disease.

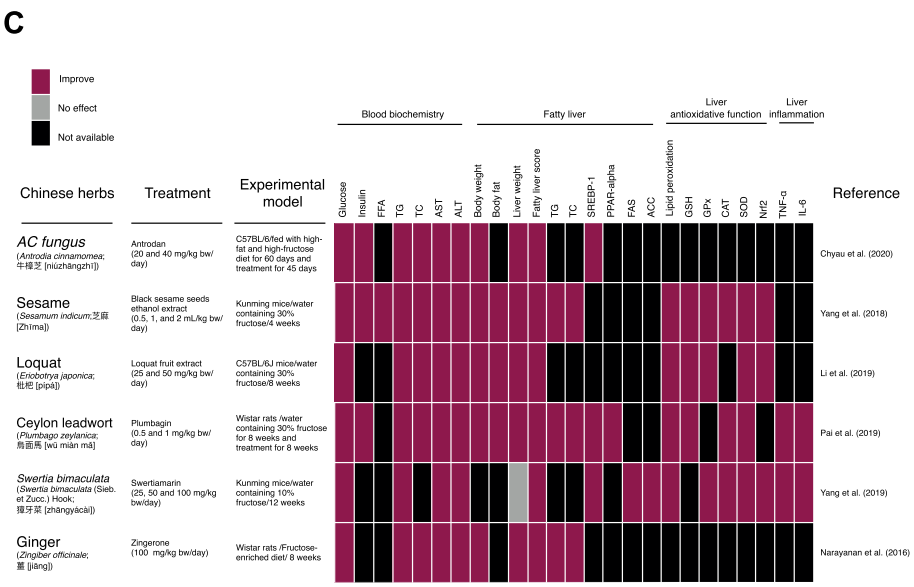

Fig. 3. (*continued*).

Declaration of competing interest

None of the authors has any conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2020.02.008.

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