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Review

Herbal medicines for the prevention of alcoholic liver disease: A review

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ABSTRACT

Ethnopharmacological relevance: Long-term excess alcohol exposure leads to alcoholic liver disease (ALD)—a global health problem without effective therapeutic approach. ALD is increasingly considered as a complex and multifaceted pathological process, involving oxidative stress, inflammation and excessive fatty acid synthesis. Over the past decade, herbal medicines have attracted much attention as potential therapeutic agents in the prevention and treatment of ALD, due to their multiple targets and less toxic side effects. Several herbs, such as *Cnidium monnieri* (L.) Cusson (Apiaceae), *Curcuma longa* L. (Zingiberaceae) and *Pueraria lobata* (*Willd.*) Ohwi (Leguminosae), etc., have been shown to be quite effective and are being widely used in China today for the treatment of ALD when used alone or in combination.
Aim of the review: To review current available knowledge on herbal medicines used to prevent or treat ALD and their underlying mechanisms.
Materials and methods: We used the pre-set searching syntax and inclusion criteria to retrieve available published literature from PUBMED and Web of Science databases, all herbal medicines and their active compounds tested on ALD induced by both acute and chronic alcohol ingestion were included.
Results: A total of 40 experimental studies involving 34 herbal medicines and (or) active compounds were retrieved and reviewed. We found that all reported extracts and individual compounds from herbal medicines/natural plants could be beneficial to ALD, which might be attributed to regulate multiple critical targets involved in the pathways of oxidation, inflammation and lipid metabolism.
Conclusions: Screening chemical candidate from herbal medicine might be a promising approach to drug discovery for the prevention or treatment of ALD. However, further studies remain to be done on the systematic assessment of herbal medicines against ALD and the underlying mechanisms, as well as their quality control studies.

Contents

Abbreviations: ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AST, aspartate aminotransferase; AOX, acyl-CoA oxidase; CAT, catalase; COX-2, cyclooxygenase-2; CPT1, carnitine palmitoyltransferase-1; CYP2E1, cytochrome P450 2E1; DGAT, diacylglycerol acyltransferase; EGCG, epigallocatechin-3-gallate; FAS, fatty acid synthase; GGT, gamma-glutamyl transferase; GPX, glutathione peroxidase; GSH, glutathione; GST, glutathione-*S*-transferase; IL-6, interleukin-6; LBP, LPS-binding protein; LPO, lipid peroxidation; LPS, lipopolysaccharide; MCAD, mitochondrial medium-chain acyl-CoA dehydrogenase; MCP-1, monocyte chemotactic protein-1; MDA, malondialdehyde; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor-κB; PGC-1α, peroxisome proliferator-activated receptor γ coactivator α; ROS, reactive oxygen species; SCD-1, stearyl CoA desaturase-1; SIRT1, sirtuin 1; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element-binding protein-1c; STAT-3, signal transducer and activator of transcription-3; TC, total cholesterols; TG, triglyceride; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRIF, TIR-domain-containing adapter-inducing interferon-β; ZO-1, zonula occludens-1

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1. Introduction

Alcoholic liver disease (ALD) is a major cause of morbidity and mortality in industrialized and developing countries, especially in China. In the initial stage of ALD, long-term heavy alcohol exposure leads to fatty liver (hepatic steatosis), characterized by triglyceride (TG) accumulation in hepatocytes, which has been widely assumed to be a benign and reversible condition (Purohit et al., 2009). However, increasing studies now demonstrated that hepatic steatosis is a potentially pathologic condition. If alcohol consumption is continued, hepatic steatosis are vulnerable to progressing to the advanced stages of ALD, such as steatohepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma, particularly in the presence of co-factors including hepatitis virus infection (Gitto et al., 2009), smoking (Kuper et al., 2000) and diabetes (Hassan et al., 2002). Despite heavy economic burden and health impact of ALD, little progress has been made in the treatment of this disease, which in part, resulted from insufficient understanding of molecular mechanisms underlying ALD (Gao and Bataller, 2011). Emerging evidence indicates that the multiple mechanisms contribute to ALD, involving oxidative stress, inflammation, excess lipid synthesis, as well as complex interactions between alcohol metabolism, lipid metabolism and the immune system (Lv et al., 2010). Moreover, one target–one drug paradigm in drug discovery has faced with unprecedented challenge (Hopkins, 2008). As a consequence, there is still no therapeutic modalities to halt or reverse the pathogenesis and progression of ALD (Kaiser et al., 2009). Use of herbal medicine to prevent various chronic diseases, including ALD, has been a common clinical practice for long in Asian countries (Ghosh et al., 2011). The therapeutic effect of herbal medicine is the comprehensive and integrated outcomes of their active components contained. Thus, the multi-targeted herbal medicines, acting on diverse factors involved in ALD, might provide an alternative approach to prevent or treat this disease. In the past decade, herbal medicines and their active compounds with less toxicity have attracted much attention as the potential agents against ALD. The aim of present review is to summarize the available experimental findings regarding herbal medicines used to prevent ALD and their underlying mechanisms, and if appropriate, to identify the most effective herbal medicine modalities for regulating ALD.

2. Search syntax and inclusion criteria

Relevant published studies were identified for the years 2002–2012 by means of a Pubmed and Web of Science search in terms of the following general string with title: (“alcoholic” OR “alcohol induced” OR “ethanol induced” OR “alcohol-induced” OR “ethanol-induced”) AND (“liver damage” OR “liver lesion” OR “liver injury” OR “fatty liver” OR “liver disease”) NOT “non-alcoholic” NOT “nonalcoholic”, a total of 253 citations were generated on April 30, 2012. The pre-set criteria for inclusion were: (i) the drugs used to prevent and treat ALD must be herbal medicine or natural plant (e.g. traditional Chinese medicine, herbal extracts) or its individual compound; (ii) only *in vivo* study was recruited; (iii) model was induced by alcohol/ethanol, rather than by other chemical agents; (iv) the study attempted to elucidate the underlying mechanism of herbal medicine; (v) only publication in English was included; and (vi) other relevant citations not included in the search syntax were manually searched.

3. Herbal medicines in the prevention and treatment of ALD

In recent decades, herbal medicines with the multi-targeted and less toxic features have attracted more attention in the prevention of ALD. In the present review, a total of 40 studies involving 34 extracts or individual compounds originated from herbal medicines/natural plants exhibited their potentially protective effect against alcohol-induced injury (Table 1). Acute or chronic alcohol-fed rats (e.g. SD rats (Lu et al., 2011), Wistar rats (Giriwono et al., 2010)) and mice (e.g. C57BL/6 (Kim et al., 2008), Kunming (Lv et al., 2010) and BALB/c (Kang et al., 2012)) were the most used experimental animals. For acute alcohol administration, the binge drinking was commonly used model by oral gavage, because this model was designed to achieve blood ethanol concentration, behavioral effects, and physiological changes comparable to those of binge drinking in humans (Carson and Pruett, 1996). For chronic alcohol exposure, the modified Lieber-DeCarli diet (36% of the total calories were supplied from alcohol) was fed animal to induce the hepatic injury.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are cytoplasmic in location and only largely released into circulation after hepatocyte structural integrity damage, thus, their activities are most commonly used as reliable markers for clinical monitoring of liver injury or liver function (Recknagel et al., 1989). Almost all herbal medicines and ingredients included, such as ethanol extract of *Antrodia cinnamomea* Chang & Chou (Polyporaceae) (reported as *Antrodia camphorata*) (Lu et al., 2011), aqueous leaf extract of *Cassia auriculata* L. (Leguminosae) (Kundu et al., 2008), curcumin (Nanji et al., 2003) and honokiol (Yin et al., 2009b), could restore the ALT and/or AST activities that elevated by alcohol exposure. Beside these biomarkers, other serum/plasma enzymes, such as alkaline phosphatase (ALP) (Lu et al., 2011) and gamma glutamyl transpeptidase (GGT) (Hou et al., 2010), were also used to assess the hepatopreventive effect of herbal medicines.

Excessive triglyceride accumulation in the liver is the common characteristic in early stage of ALD. Abnormal retention of lipids within hepatocyte leads to liver damage. Several herbal medicines and individual compounds (Fig. 1) are able to protect against hepatic steatosis induced by acute or chronic alcohol intake, as assessed by the determination of hepatic TG level and/or histological tests, such as H&E or Oil red O staining. For example, pretreatment with cinnamon bark extract (Kanuri et al., 2009) and anthocyanin-rich extract from *Oryza sativa* L. Japonica (Poaceae) (500 mg/kg) (Hou et al., 2010) prior to alcohol ingestion significantly inhibited lipid accumulation in liver by 45% and 78.6%, respectively. Alcohol-induced hepatic TG accumulation also could be fully reversed by individual compounds, such as