Review Article

Dietary supplementation in patients with alcoholic liver disease: a review on current evidence

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BACKGROUND: Alcoholic liver disease (ALD) is one of the main causes of liver disease worldwide. Although the pathogenesis of ALD has not yet been well elucidated, the oxidative metabolites of ethanol such as acetaldehyde and reactive oxygen species play a pivotal role in the clinical and pathological spectrum of the disease. This review summarizes the existing evidences on dietary supplements considered to have antioxidant, and/or anti-inflammatory properties, and their role in the management of ALD and the proposed mechanisms.

DATA SOURCES: The present study reviewed all studies published in PubMed, ScienceDirect and Scopus, from 1959 to 2015, indicating the role of different dietary supplementation in attenuation of many pathophysiological processes involved in development and progression of ALD. Full-texts of citations were used except for those that were published in languages other than English.

RESULTS: Significant progress has been made to understand the key events and molecular players for the onset and progression of ALD from both experimental and clinical studies; however, there is no successful treatment currently available. The present review discussed the role of a variety of dietary supplements (e.g. vitamin A, carotenoids, vitamins B3, C and E, in addition to antioxidants and anti-inflammatory agents) in treating ALD. It has been shown that supplementation with some carotenoids, vitamin B3, vitamin C, silymarin, curcumin, probiotics, zinc, S-adenosylmethionine and garlic may have potential beneficial effects in animal models of ALD; however, the number of clinical studies is very limited. In addition, supplementation should be accompanied with alcohol cessation.

CONCLUSIONS: Since oxidative stress and inflammation are involved in the pathogenesis of ALD, dietary supplements that can modulate these pathologies could be useful in the treatment of ALD. In addition to alcohol cessation, these supplements have shown beneficial effects on animal models of ALD. Clinical trials are needed to validate the beneficiary role of these supplements in patients with ALD.

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KEY WORDS: alcoholic liver disease; fatty liver; dietary supplements; antioxidants; nutrition; diet

Introduction

Too much alcohol consumption is related to several chronic disorders such as alcoholic liver disease (ALD), cancers, and cardiovascular diseases[1] so that it is known as a main cause of morbidity and mortality worldwide.[2-6] The drinkers have a lot of histological abnormalities in their livers due to alcohol toxic effects including steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma.[3-7] It has been shown that there is a positive correlation between cumulative alcohol intake and severity of liver fibrosis.[4] Approximately 3.8% of total deaths and 4.6% of disability-adjusted life-years in the world are associated with alcohol consumption. Burden of disease for every unit of alcohol consumption is higher in poor communities and low-income nations than in the middle-income communities and wealthy countries.[8]

Not only too much alcohol intake can result in severe damage in the liver, but also in the heart, kidney, nervous system and pancreas.[4, 7] In addition, excessive alcohol consumption increases the progression of other liver

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diseases, such as chronic viral hepatitis (hepatitis B and C) and other metabolic liver diseases, including Wilson disease, hemochromatosis, and fatty liver in relation to the metabolic syndrome.[4, 5]

Previous studies[4, 9, 10] indicated that acetaldehyde, an intermediate alcohol metabolite, is a highly reactive compound and highly toxic to hepatocytes; it depletes glutathione, enhances lipid peroxidation, and mitochondrial damage, which leads to oxidative stress. Furthermore, alcohol-derived reactive oxygen species (ROS) may directly trigger the systemic inflammatory response. ROS could activate nuclear factor kappa B (NF-κB), which results in production of inflammatory cytokines such as TNF-α and IL-6. Alcohol-derived ROS may initiate a vicious cycle via the hepatocyte damage mechanism with additional inflammatory cytokines and ROS production.[3, 11-14] Moreover, alcohol consumption increases the small intestinal bacterial overgrowth and intestinal permeability of endotoxins. The endotoxin mediated inflammatory signaling plays a major role in alcoholic liver fibrosis.[11, 15]

Although alcohol intake is the major risk factor for ALD, interactions between behavioral, environmental, and genetic factors are also involved in its pathogenesis. The other known risk factors include age, gender, obesity and a higher BMI, dietary factors, drinking patterns, cigarette smoking, and non-gender-linked genes; however, the mechanism of their affects has not yet elucidated.[4] A recent study[2] showed that some metabolic factors, such as metabolic syndrome, insulin resistance and type 2 diabetes are related to the development and progression of ALD. Several epidemiological studies[3-6] suggested that some genetic factors are involved in the severity of steatosis and oxidative stress. The previous studies on genome-wide association found that the patatin-like phospholipase-3 (PNPLA3) rs738409 variant may act as the first genetic risk factor for increased activity of aminotransferase, development of steatohepatitis, fibrosis and cirrhosis, and ultimate progression of ALD in the subjects who consumed alcohol.[16-18] Thus, the PNPLA3 (also known as adiponutrin) rs738409 genotype can be used as a genetic marker for detection of hereditary susceptibility of an individual to develop ALD.[17]

No treatment has yet been approved for patients with ALD and the only recognized management strategies include alcohol cessation;[4, 6, 7] therefore, development of novel pathophysiological-targeted adjuvant therapies is urgently needed.[19] Dietary supplements are suitable therapeutic options due to their antioxidant, and anti-inflammatory properties. Thus we reviewed the publications available so as to evaluate the effects of dietary supplements in ALD management.

Dietary supplementation in ALD management

Vitamins

Patients with ALD have low intakes of various nutrients including vitamins. Moreover, chronic alcohol abuse can impair gastrointestinal mucosal absorption of micronutrients such as folate, vitamin B12, zinc, vitamin A, thiamine, and pyridoxine.[20] Pyridoxine deficiency occurs because acetaldehyde causes a competitive decline in albumin binding and leaves the unbound vitamin to be lost in urine.[20] McClain et al[9] reported that plasma concentrations of zinc, carotene, and selenium are significantly decreased in patients with ALD. Thus, it seems that patients with ALD benefit from supplementation of vitamins and minerals.

Vitamin A and carotenoids

ALD is related to low levels of hepatic vitamin A, and the reduction of hepatic retinoid content is correlated with disease severity.[21-24] Supplementation with β-carotene may revive the vitamin A status to a normal range, resulting in protection against alcohol-related liver injury.[20, 24] Lutein has a protective role in combating liver damage caused by hepatotoxins. This hepatoprotective action may be due to lutein's ability to scavenge ROS.[25] Moreover, lutein prevented alcohol-induced lipid accumulation through increasing lipogenic genes expression.[26] A low dose of β-carotene supplementation decreased oxidative stress through reducing CYP2E1 gene expression, inhibiting lipid peroxidation and glutathione peroxidase concentrations in erythrocytes and the liver. Therefore, β-carotene prevents ethanol-induced liver damage;[27, 28] but the beneficial effect of the high dose of β-carotene has not been confirmed.[28, 29] It has been shown that the level of plasma β-carotene was increased in heavy alcohol consumers and decreased in patients with alcoholic cirrhosis. Thus, supplementation should be accompanied with alcohol cessation.[30] Clinical trials considering the amount of alcohol consumption are recommended.

Vitamin C

Vitamin C is known as an independent antioxidant, which can protect against ALD progression to liver fibrosis[31] through decreasing oxidative stress, hepatic stellate cells activation, cytotoxicity and fibrotic genes expression in liver tissues.[32] Moreover, vitamin C reduced the endotoxin level by mitigation of small intestinal bacterial overgrowth, and concomitant endotoxemia. The reduction of endotoxin decreased nuclear translocation of NF-κB and thereby reduced the signal cascade, thus leading to the suppression of hepatic stellate cells activation and

collagen deposition and finally liver fibrosis.[15] Furthermore, vitamin C ameliorates the progression of ALD by regulating the expression of iron metabolism-related genes.[33] There is no clinical trial evaluating the effects of vitamin C supplementation on ALD.

Vitamin E

Vitamin E supplementation can be a potential therapeutic substance for alcohol-induced hepatotoxicity as well as oxidative damages in the liver;[10, 34, 35] however, the beneficial effects of vitamin E in human ALD subjects have not yet been confirmed. Altavilla et al[36] reported that raxofelast, an analog of vitamin E, can protect mice from ALD and ameliorate liver damage by inhibiting the inflammatory cascade during chronic ethanol exposure. Mezey et al[37] demonstrated that 1000 IU/day of vitamin E in three months decreased serum hyaluronic acid, an indicator of fibrosis but did not result in significant improvements in serum bilirubin and serum albumin as measures of liver function and had no benefit in decreasing serum aminotransferases, indicators of hepatocyte necrosis and inflammation, or on parameters reflecting evidence of oxidative stress or lipid peroxidation. However, the effect of vitamin E on ALD is inconclusive. A meta-analysis[38] demonstrated that consuming more than 400 IU/day (high dosage) of this supplement may increase the rate of mortality. Further clinical trials with different dosages and longer duration are needed.

Vitamin D

Chronic alcoholism results in deficiency of osteocalcin, vitamin D and insulin growth factor-1 and thus endocrine dysfunction and bone mass reduction.[39-41] Malnutrition, malabsorption, decreased production of vitamin D binding protein in the liver, weakened hepatic hydroxylation of vitamin D, as well as insufficient exposure to sunlight and consequently reduced dermal production of vitamin D are the known causes of vitamin D deficiency in ALD.[42] It has been reported that reduced serum level of 25(OH)D may aggregate liver injury and result in elevated mortality rates in ALD. Therefore, it has been proposed that vitamin D level can be a valuable indicator of ALD progression and can be used as a potential agent in the treatment of ALD.[43, 44] A clinical trial showed that vitamin D3 provides greater efficacy in improving the symptoms of vitamin D deficiency compared with vitamin D2.[45]

Vitamin B3

Only one experimental study has evaluated the effects of nicotinic acid supplementation in ALD, which has shown that nicotinic acid can protect against ALD through increasing hepatic fatty acid oxidation and reducing *de novo* lipogenesis in the liver.[46]

Antioxidant and anti-inflammatory agents

Silymarin

Silymarin is a mixture of antioxidant flavonolignans (silybin and silibinin) extracted from the medicinal plant *Silybum marianum*. Experimental studies[47-49] have shown that silymarin protects against liver damage via its antioxidant and anti-fibrotic effects; moreover, it is an excellent immune modulator and cell membrane stabilizer, as well as inducer of liver tissue regeneration. It demonstrates positive effects on ALD by retarding the development of fibrosis and inhibiting hepatic NF-κB activation and pro-collagen-α1 gene expression.[48-51] Furthermore, it has been shown that silymarin increases the expression of antioxidant enzymes, normalizes liver enzymes, and improves insulin activity.[47, 52-55] However, it did not effectively prevent the carcinogenesis in animal models of ethanol-dependent hepatocellular carcinoma.[56] A retrospective study[57] has shown the beneficial effects of a silymarin product on liver enzymes and serum liver function. However, randomized, placebo controlled, clinical trials are needed to confirm these effects. The safety for silymarin as well as its excellent pharmacokinetics and antioxidant activity has made this agent as a perfect dietary supplement for people who are suffering from ALD. Furthermore, the consumption of this supplement during pregnancy and lactation is safe due to its feto-protective and prolactin stimulatory effects.[58, 59]

Curcumin

Curcumin is a polyphenol constantly approved as an antioxidant and an anti-inflammatory substance.[60] It has great protective impact on acute alcoholic liver damages in mice, and can improve the antioxidant activity of mice after acute administration of alcohol. It can increase the activity of antioxidant enzymes in liver tissues.[61] Curcumin prevented ethanol-induced liver damage by inhibiting oxidative stress and lipid accumulation;[62] however, there is no clinical trial to assess its effects in patients with ALD.

Resveratrol

Resveratrol is a polyphenolic compound with antioxidant properties, which has beneficial effects on down-regulation of inflammatory mediators and metabolic disorders.[63] Resveratrol can inhibit the ethanol-induced lipid peroxidation, reduce lipid synthesis and increase rates of fatty acid oxidation. It has protective effect against alcohol-induced cell apoptosis as well as oxidative damage and alcoholic liver steatosis.[64-68] Our previ-

ous studies[63, 69] have shown its beneficial effects in patients with nonalcoholic fatty liver disease in a clinical trial although there is no clinical trial on patients with ALD.

Citrus flavonoids

Limited studies have shown that citrus flavonoids such as hesperidin and narirutin could reduce the accumulation of hepatic lipid through modulation of the antioxidant status, and thereby inhibiting hepatic inflammation and necrosis.[70, 71] Further studies, especially clinical trials, are needed.

Tea polyphenols

Tea polyphenols are able to inhibit the intestinal alcohol absorption; moreover, they inhibit the progression of ALD via reduction of oxidative stress and inflammatory reactions through regulation of antioxidative pathways. They also inhibit NF-κB activation and gene expression of hepatic inflammatory cell cytokines.[72-76] There are no adequate data showing the optimal dosage and type of tea consumption for the management of ALD. Clinical trials using different dosages and types of tea can help to find the optimum dose and type of tea for the management of ALD.

Probiotics

Alcohol and its metabolites disturb the intestinal microflora, and its epithelial barrier function. When the pathogenic bacteria increase in the gut, the intestinal permeability is disturbed so that more microflora derived lipopolysaccharide can pass the intestinal epithelial tight junctions, resulting in more inflammation and oxidative stress.[11, 77] Thus, the modulation of gut microflora to reduce the lipopolysaccharide load might play a pivotal role in ALD management. Consumption of probiotics and/or prebiotics is one of the best ways for modulation of gut microbiota.[78, 79] Probiotics modulate the production of intestinal microbiota and endotoxin and enhance intestinal barrier function, thus leading to the reduction of bacterial translocation and the decrease of hepatic inflammation.[77, 78, 80-85] We have revealed the beneficial effects of probiotics on nonalcoholic fatty liver disease characteristics.[86] Moreover, it has been shown that probiotic supplementation improves neutrophil function in patients with alcoholic cirrhosis, although it does not affect the mortality.[87] More randomized, placebo controlled, clinical trials are needed to confirm these results.

Zinc

Since ethanol consumption increases zinc excretion in the urine and decreases zinc absorption from the intestine,[88, 89] zinc depletion has been well documented in alcoholic patients as well as in animal models of ethanol-induced liver injury. Zinc depletion is exacerbated by the increasing severity of ALD.[90-93] Zinc deficiency disturbs the integrity of the intestinal epithelium leading to bacterial translocation and hepatic inflammation at last.[11, 94] In experimental models of ALD, zinc supplementation suppressed hepatic TNF-α production in association with decreased circulating endotoxin levels and a significant protection of the structure of the small intestine,[95, 96] and significantly inhibited acute ethanol-induced liver injury.[95-100] Zinc inhibits the generation of ROS, and enhances the activity of antioxidant pathways.[97, 99, 100] It has been proposed that zinc is a potent inhibitor of liver apoptosis induced by acute ethanol administration. Zinc interferes with the Fas ligand pathway and the suppresses caspase-3.[101] No clinical trial has yet evaluated the effects of zinc supplementation on ALD characteristics.

S-adenosylmethionine (SAM)

Alcohol interferes with methionine metabolism through inhibition of methionine adenosyltransferase activity, which reduces the levels of SAM and glutathione, increases oxidative stress, and exacerbates ALD.[19, 102, 103] Depletion of SAM impairs antioxidant defense, changes the genes expression, promotes fibrogenesis and even hepatocarcinogenesis.[13, 19, 102-105] *In vitro* and *in vivo* studies[102, 106, 107] showed that SAM and betaine (precursor to SAM) potentially alleviate ALD via the restoration of transmethylation and transsulfuration pathways of methionine metabolism and improve liver steatosis and oxidative liver injury. In clinical trials,[108-110] SAM increases cellular antioxidant glutathione in patients with ALD and improves the survival of patients with less advanced liver cirrhosis; however, its effectiveness has not been confirmed in patients with ALD. These controversial results might be due to the role of other nutrients, that are involved in methionine adenosyltransferase activity such as folate, vitamin B6 and B12. Thus, other nutritional factors involved in SAM metabolism should be considered in larger and longer clinical trials.[12, 105, 111]

Garlic

Chemical constituents of garlic are enzymes (e.g. alliinase) and organosulfur compounds (e.g. alliin and its derived agent allicin). Garlic effect on different medical conditions (such as hypertension, hyperlipidemia, diabetes mellitus, rheumatic disease, common cold, and arteriosclerosis and cancer) has been widely investigated. Garlic is generally safe and well tolerated and has no adverse effects on allergic patients.[112] Garlic is known as a hypolipidemic agent because of its role in increasing the hydrolysis of triacylglycerols due to increased lipase

activity. Moreover, garlic reduces the biosynthesis of triacylglycerols via blocking nicotinamide adenine dinucleotide phosphate. On the other hand, garlic contains abundant antioxidants, and can induce antioxidant enzymes. Thus, garlic is a potential hepatoprotective agent against liver disorders such as ALD.[113, 114] Experimental studies have shown that garlic and its organosulfur compounds might reduce the alcohol-related liver enzymes, glutathione reductase, alkaline phosphatase, lactate dehydrogenase and alcohol dehydrogenase, enhance liver antioxidant enzymes, and alleviate hepatic fat accumulation.[14, 113-120] However, there is no clinical trial on patients with ALD.

Soy protein

Soybean contains many bioactive components such as soy protein and soy isoflavones. It has been demonstrated that soy protein has hepatoprotective effects on alcohol-induced lipid accumulation, oxidative stress and inflammation.[121, 122] Clinical trials are necessary to examine the effects of soy protein and its substitution with animal protein intake on ALD characteristics.

Table presents each of the selected studies for this review, showing study description, supplementation protocol, dose and duration, and the proposed mechanism of action of the intervention.

Nutritional therapies

Based on the severity of ALD, providing an adequate diet can strongly slow the disease progression, reduce serious complications, delay liver transplantation, and decrease mortality rate. Nutritional therapies in patients with ALD should aim at preventing alcohol-induced malnutrition, providing adequate daily requirements and reducing hypermetabolism. Dietary supplementation may be required for ALD patients who cannot eat adequately.[20, 123] Because of the disturbed glucose homeostasis in the liver as a result of chronic alcohol consumption, starvation or long-term fasting should be avoided in the patients with ALD. Thus, intake of frequent meals is necessary to prevent alcohol-induced hypoglycemia. Administration of 2-3 mg/kg intravenous glucose per day may be required in case of fasting for ≥12 hours.[20] According to the guidelines of European Society for Clinical Nutrition and Metabolism (ESPEN), the daily requirements of protein and energy in cirrhotic patients are about 1.2-1.5 g/kg and 35-40 kcal/kg per day, respectively. Enteral nutrition support is recommended in the patients with inadequate oral nutritional intake.[124] In spite of the previous belief, protein restriction in cirrhotic patients is not recommended because it may result in muscle wasting, exacerbation of hepatic encephalopathy, and rise in blood ammonia.[125]

Table. Dietary supplementation in ALD management

Studies	Study description, dose, duration	Supplement proposed mechanism of action/overall conclusion
Kaur et al[10]	Male Balb/c mice Vitamin E 5 IU/kg	Diminished apoptosis Inhibited oxidative stress Blunted the increased activity of NF-κB Up-regulated AP1 expression
Ki et al[14]	Sprague-Dawley rats Metadoxine and garlic oil (MG) combination (15, 50 or 100 mg/kg per day each) 6 days	Ameliorated fat accumulation in the liver via CYP2E1 repression Restored the FAS level and AMPK phosphorylation
Abhilash et al[15, 32]	Male guinea pigs Ascorbic acid (AA) 250 mg/kg b.wt daily 30 days	Recovered alcohol-induced liver fibrosis faster than abstention through down-regulating the α-SMA, caspase-3 and mRNA levels of CYP2E1, TGF-β, TNF-α, and α1(I)collagen and mediating nuclear translocation of NF-κB which resulted in suppressing HSCs activation, apoptosis and interstitial collagen synthesis in liver Decreased the endotoxin level by reduction of SIBO and intestinal barrier defect
Sindhu et al[25]	Male Wistar rats Lutein 100-250 mg/kg	Decreased the liver tissue damage through antioxidant activity
Liu et al[26]	Male C57BL/6 mice Luteolin 50 mg/kg	Inhibited hepatic fat accumulation by promoting expression of the lipogenic genes
Lin et al[27]	Male Sprague-Dawley rats Diet containing 10% β-carotene 10 weeks	Decreased AST and ALT levels Elevated GSH concentrations in erythrocytes and the liver Inhibited ethanol-induced liver damage

(To be continued)

Studies	Study description, dose, duration	Supplement proposed mechanism of action/overall conclusion
Peng et al[28]	Male Wistar rats β-carotene 0.52-2.6 mg/kg 12 weeks	Reduced oxidative stress via: -Reducing CYP2E1 gene expression -Preventing lipid peroxidation -Increasing GPx concentrations in erythrocytes Inhibited ethanol-induced liver damage
Portari et al[29]	Male Wistar rats Diet containing 0.5g% β-carotene 28 days	No beneficial antioxidant effect
Ahmed et al[30]	30-60 mg/d β-carotene 5 alcoholics without cirrhosis, and 7 patients with cirrhosis, 5 control subjects 3 days	Due to probable hepatotoxic interactions between alcohol and β-carotene, β-carotene supplementation, in combination with control of drinking can be beneficial especially in cirrhotic patients
Guo et al[33]	Male Kun-Ming mice Vitamin C 50-100 mg/kg daily 7 days	Lowered ALT activity and iron overload in the liver Increased the expression of hepcidin and decreased transferrin receptor 1 (TfR1) expression in the liver Stimulated ferroportin 1 (Fpn1) expression in the intestine and diminished iron release to blood
Pirozhkov et al[34]	Male C57BL/mice Vitamin E 20-170 IU/L	The diet containing 170 IU/L vitamin E improved the hepatotoxicity Improved collagen accumulation
Das et al[35]	Male Balb/c mice Both resveratrol 5 mg/kg per day and vitamin E 80 mg/kg per day	Attenuated the activities of AST, ALT, GST, IL-10, TNF-α, IFN-gamma, VEGF-A and TGF-β1 and TBARS and nitrite levels Improved SOD, CAT, GR and GPx activities, albumin content, and GSH level
Altavilla et al[36]	Female C57BL/6 mice An analog of vitamin E (raxofelast) 20 mg/kg per day	Prevented NF-kappaB activity Diminished the levels of ALT, triacylglycerols, hepatic MDA levels, prevented liver GSH depletion and decreased TLR-4, TNF-α, IL-6 and ICAM-1 hepatic gene expression Ameliorated liver damage Blunted the inflammatory cascade and organ damage during chronic ethanol exposure
Mezey et al[37]	25 patients, 26 controls Vitamin E 1000 IU/d 3 months	Lowered serum hyaluronic acid
Malham et al[45]	300 000 IU ergocalciferol (D_2 group, n=23) or cholecalciferol (D_3 group, n=13)	A single oral megadose of cholecalciferol has more therapeutic effects on ALD patients with vitamin D deficiency compared to ergocalciferol
Li et al[46]	Male Sprague-Dawley rats Nicotinic acid (NA) 750 mg/L 8 weeks	Improved hepatic fat accumulation through lowering the expression of hepatic fatty acid synthase Increased serum β-hydroxybutyrate and adiponectin Increased the content of total NAD, NAD(+), and NADH in the liver Elevated cytochrome P450 4A1 (CYP4A1) and acyl-coenzyme A oxidase 1 in the liver Diminished the ubiquitination level of CYP4A1
Jia et al[48]	Female Wistar rats Silymarin 50 mg/kg per day	Inhibited expression of profibrogenic procollagen alpha1(I) and TIMP-1 possibly by suppressing the TGF-β1 mRNA expression Lowered the serum procollagen type III propeptide level which is an indicator of the hepatic profibrogenic mRNA expression
Lieber et al[49]	Twelve baboons Silymarin 39.81 mg/kg 3 years	Reduced alcohol-induced oxidative stress Improved the rise in liver lipids and serum ALT activity Inhibited the elevation of hepatic collagen type I and alpha1 (I) procollagen mRNA Restored the expansion of liver fibrosis
Fehér et al[52]	*In vitro* incubation with the usual therapeutic dosage of silymarin as well as *in vivo* study	*In vitro* incubation with the usual therapeutic dosage of silymarin: elevated the SOD expression of lymphocytes and erythrocyte and lymphocyte SOD activities. *In vivo* treatment: enhanced the activity and expression of SOD in lymphocytes and erythrocytes

(To be continued)

Studies	Study description, dose, duration	Supplement proposed mechanism of action/overall conclusion
Müzes et al[53]	420 mg/d silymarin administration in patients with ALD 6 months	Elevated the serum level of ree--SH groups and the activity of GPx Reduced serum MDA Improved the initially low SOD activity of erythrocytes and lymphocytes
Fehér et al[54]	Silymarin administration on 36 ALD patients 6 months	Normalized serum level of AST and ALT Lowered the activity of GGT and procollagen III peptid level Ameliorated the histological changes in the liver
Lirussi et al[55]	42 outpatients 135 mg/d silybin *per os* 6 months	Reduced plasma levels of glucose and triglyceride
Brandon-Warner et al[56]	*In vivo* and *in vitro* Male and female B6C3 mice 0.5% (*w/w*) silibinin 9 weeks	Did not effectively prevent the development of hepatic tumor
Nanda et al[57]	A retrospective study of 602 patients who received water soluble silymarin (Liverubin™) treatment 11 months	Improved hepatic enzymes and serum liver function tests It was safe, effective and well-tolerated in the doses of 140 mg three times a day
Zeng et al[61]	Male Kun-Ming mice Curcumin 50, 100 and 200 mg/kg 14 days	Enhanced serum AST and ALT activity at high-dose group Increased the hepatic activity of SOD, GSH-Px and antioxidative capacity Diminished the content of MDA
Rong et al[62]	Balb/c mice Curcumin 75 mg/kg per day 6 weeks	Exerted hepatoprotective effects through preventing oxidative stress and lipid accumulation
Bujanda et al[64]	Male Balb/c mice 10 mg/mL water resveratrol 6 weeks	Decreased mortality and liver by its antioxidant, anti-inflammatory and anti-infectious actions
Kasdallah-Grissa et al[65]	Wistar rats 5 g/kg resveratrol 6 weeks	Suppressed hepatic lipid peroxidation and inhibited the oxidative damage by ameliorating SOD, GPx and CAT activities in the liver
Ajmo et al[66]	C57BL/6J mice 200-400 mg/kg resveratrol per day 4 weeks	Prevented alcoholic liver steatosis by ameliorating lipid synthesis and rates of fatty acid oxidation Up-regulated SIRT1 expression levels and increased hepatic AMPK activity by suppression of SREBP-1 and activation of PGC-1alpha
Raal et al[68]	Male Balb/c 20 mg/kg trans-resveratrol per day 35 days	Prevented of oxidation of polyunsaturated fatty acids
Park et al[70]	Male ICR mice 325 mg citrus flavonoids (CFs)/kg (60% hesperidin and 40% narirutin) 8 weeks	Suppressed increases in prognostic parameters of a hepatocellular injury and proinflammatory cytokines such as IκB-α, TNF-α, IL-1β and IL-6 Inhibited excessive lipid formation Improved the antioxidant defense
Park et al[71]	Male ICR mice Citrus narirutin fraction (CNF) 150-300 mg CNF/kg 8 weeks	Lowered serum ALT and AST activity Suppressed excessive liver triglyceride and total cholesterol accumulations Normalized SOD activity, GSH and MDA levels Inhibited hepatic production of NF-κB, TNF-α and IL-1β in a dose-dependent manner
Zhang et al[73]	Male Sprague-Dawley rats Tea polyphenols (250 mg/kg per day) 12 weeks	Stimulated the gene expressions of IL-3, IL-4, IL-1R2, IL-6R, IL-7R2 Suppressed the gene expressions of IL-3Ra, IL-1R1 Improved alcohol-induced liver damage
Zhang et al[74]	Male Sprague-Dawley rats 0.25 g/kg tea polyphenols 24 weeks	Lowered serum ALT and AST activities Ameliorated the pathological changes
Li et al[76]	Sprague-Dawley rats Tea polyphenols (0.05, 0.125, 0.25 g/kg) 24 weeks	Attenuated liver fibrosis by the antioxidative pathway and decreasing endotoxin level

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Studies	Study description, dose, duration	Supplement proposed mechanism of action/overall conclusion
Kirpich et al[78]	66 males patients /24 healthy control *Bifidobacterium bifidum* and *Lactobacillus plantarum* 5 days	Decreased AST and ALT, GGT, LDH, and total bilirubin
Bang et al[82]	C57BL/6 mice 1 mg/mL per day of *L. rhamnosus* R0011 and *L. acidophilus* R0052 10 weeks	Down-regulated the expression of TLR-4 Reduced hepatic IL-1β levels
Segawa et al[84]	C57BL/6 mice Heat-killed *L. brevis* 100-500 mg/kg per day 35 days	Suppressed the overexpression of TNF-α, SREBP-1, and SREBP-2 mRNA in the liver Stimulated the expression of Hsp25 mRNA in the small intestine
Zhao et al[85]	Male C57BL/6N mice *Lactobacillus rhamnosus* GG (LGG) 109 CFU/d/mouse 4 weeks	Inhibited ethanol-induced liver damage by - Suppressing the expression of miR122a - Stimulating the expression of epithelial tight junction protein occludin - Lowering endotoxemia - Promoting intestinal barrier function
Stadlbauer et al[87]	12 patients with alcoholic cirrhosis, 21 control subjects *Lactobacillus casei Shirota* (6.5×10^9): 3 times daily 4 weeks	Normalized neutrophil phagocytic capacity in cirrhosis, through ameliorating IL-10 secretion and TLR-4 expression
Lambert et al[95]	Metallothionein knockout (MT-KO) mice 2.5 mg zinc ion/kg	Promoted intestinal structural integrity through inhibition of endotoxemia and liver damage in an MT-independent manner
Lambert et al[96]	Male 129 SvPCJ mice 5 mg of zinc ion/kg	Prevented alcohol-induced intestinal hyperpermeability which lead to ameliorating liver injury
Zhou et al[97]	Metallothionein-knockout and wild-type 129/Sv mice 75 mg zinc element/L 12 weeks	Ameliorated alcohol-induced liver damage independent of MT via preventing the generation of reactive oxygen species (P450 2E1) and enhancing the antioxidant activity
Zhou et al[98]	MT I/II-knockout (MT-KO) mice 5 mg/kg zinc per day 3 days	Improved alcohol-induced liver damage by enhancing the activity of antioxidant defense
Xiao et al[99]	C57BL/6 mice 75 mg/L zinc sulfate 6 months	Elevated HNF-4α which lead to restoration of the liver damage
Kang et al[100]	Male 129S mice 75 mg elemental zinc/L zinc sulfate in liquid diet 4 weeks	Restored alcohol-reduced white adipose tissue mass which lead to decreased hepatic fat accumulation Stimulated HNF-4α and PPAR-α Improved alcoholic steatosis via ameliorating fatty acid β-oxidation and VLDL secretion
Lambert et al[101]	Male 129/Sv(PC)J mice 5 mg of zinc ion/kg In 12-hour intervals for 36 hours	Prevented alcohol-induced liver apoptosis via suppression of Fas ligand activation and inhibition of caspase-3 and caspase-8
Jung et al[107]	Male Wistar rats 1% (*w/v*) betaine 6 weeks	Enhanced liver steatosis and oxidative liver damage through enhancing sulfur amino acid metabolism Increased SAM level which resulted in the suppression of Kupffer cell activation and improvement of liver antioxidant capacity Elevated cysteine synthesis suppressed its catabolism to taurine, which result in promoting GSH generation and antioxidant defense Restored the alcohol-induced liver damage
Vendemiale et al[108]	9 patients with ALD/23 control subjects 1.2 g/day SAM 6 months	Promoted hepatic GSH levels
Mato et al[109]	123 patients 1200 mg/d SAM 2 years	Enhanced survival and delayed liver transplantation especially in the earlier stages of the liver disease

(To be continued)

Studies	Study description, dose, duration	Supplement proposed mechanism of action/overall conclusion
Medici et al[110]	37 patients with ALD 1.2 g/d SAM 24 weeks	No beneficial effect
Raghu et al[113]	Male C57BL/6 mice Garlic oil (GO) (50 mg/kg) or diallyl disulfide (DADS) (15 mg/kg) 4 weeks	Both: improved the serum levels of ALT and AST, liver antioxidant enzymes and decreased hepatic contents of triglycerides and cholesterol DADS: involved in arachidonic acid metabolism, altered T cell and B cell signaling, tryptophan metabolism, antigen presentation pathway GO: involved in metabolism of xenobiotics, mitotic roles of polo-like kinase, fatty acid metabolism, LPS/IL-1 mediated inhibition of RXR function, and C21-steroid hormone metabolism
Zeng et al[115]	In the *in vitro* study: human normal cell L02 In the *in vivo* study: male Kun-Ming mice, single dose of GO (50-200 mg/kg)	Attenuated the n-SREBP-1c and CYP2E1 protein levels and elevated PPAR-α protein levels which lead to improvement in liver steatosis Decreased the protein levels of FAS Enhanced hepatic mitochondrial dysfunction
Zeng et al[117]	Male Kun-Ming mice GO (50, 100 and 200 mg/kg)	Improved liver steatosis via its antioxidant actions when it was administrated before or simultaneously with ethanol exposure No beneficial effect was detected when it was administrated after ethanol exposure
Kim et al[120]	Male Sprague-Dawley rats 100 mg/kg aged black garlic (ABG) 4 weeks	Attenuated hepatic fat accumulation and activities of AST, ALT, ALP and LDH in the liver Lowered cytochrome P450 2E1 activity Elevated the activities of GST and quinine reductase Reduced TBARS level Attenuated the oxidative damage to blood lymphocyte DNA
Park et al[121]	Male Sprague-Dawley rats 1 g/kg/d soy 11S protein extract 6 weeks	Lowered serum ALT and AST levels Decreased total cholesterol and total lipid levels Enhanced important hepatocyte structures
Yang et al[122]	Male Wistar rats Diet containing 41.4 g/L soy protein isolate 4 weeks	Ameliorated fat accumulation in the liver and improved oxidative stress and inflammation through suppression of proinflammatory cytokines and CYP2E1 protein expression Elevated PPARα and CYP4A protein expressions and fecal lipid excretion

AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; GSH: glutathione; GGT: alanine gamma-glutamyltransferase; GST: glutathione-S-transferase; GPx: glutathione peroxidase; GR: glutathione reductase; SOD: superoxide dismutase; CAT: catalase; MDA: malondialdehyde; TBARS: thiobarbituric acid reactive substance; SREBP-1: sterol regulatory element binding protein 1; PPARα: peroxisome proliferator-activated receptor-α; PGC-1alpha: peroxisome proliferator-activated receptor gamma coactivator alpha; SIRT1: sirtuin 1; AMPK: AMP-activated kinase; TLR-4: Toll-like receptor-4; MT: metallothionein; FAS: fatty acid synthase; IFN-gamma: interferon gamma; TNF-α: tumor necrosis factor α; NF-κB: nuclear factor-κB; IL: interleukin; HSCs: hepatic stellate cells; SIBO: small intestine bacterial overgrowth; SAM: S-adenosylmethionine; HNF-4α: hepatocyte nuclear factor 4 alpha.

Conclusion

There is currently no satisfying treatment available for patients with ALD; dietary supplements have shown beneficial effects in animal models of ALD and might be useful in clinical practice. Dietary supplements have antioxidative and anti-inflammatory effects and therefore, potentially alleviate liver injury in patients with ALD. However, further clinical trials are needed to validate the role of dietary supplements in patients with ALD.

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