Name of journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13580

Columns: Topic Highlight

WJH 6th Anniversary Special Issues (7): Nonalcoholic fatty liver disease

**Recent advances in dietary supplementation, in treating non-alcoholic fatty liver disease**

Eslamparast T *et al.* Recent advances in dietary supplementation

Tannaz Eslamparast, Sareh Eghtesad, Hossein Poustchi, Azita Hekmatdoost

**Tannaz Eslamparast, Azita Hekmatdoost,** Department of Clinical Nutrition and Diet Therapy, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Science, PO Box 19395-4741, 1981619573 Tehran, Iran

**Tannaz Eslamparast, Sareh Eghtesad, Hossein Poustchi,** Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, PO Box 14117-13135 Tehran, Iran

**Author contributions:** All authors contributed to this work.

**Correspondence to: Dr. Azita Hekmatdoost,** Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Science, 7 No, West Arghavan St., Farahzadi Blvd., PO Box 19395-4741, 1981619573 Tehran, Iran. a\_hekmat2000@yahoo.com

**Telephone:** +98-21-22360658 **Fax:** +98-21-22360657

 **Received:** August 27, 2014 **Revised:** November 9, 2014

**Accepted:** November 17, 2014

**Published online:**

**Abstract**

Nonalcoholic fatty liver disease (NAFLD) is currently known as the most common liver problem, characterized by excessive lipid accumulation in hepatocytes, which may progress to other liver diseases such as nonalcoholic steatohepatitis, hepatic tissue fibrosis, liver cirrhosis, and failure or hepatocellular carcinoma. Since NAFLD is positively associated with the development of obesity, insulin resistance, and ultimately type 2 diabetes mellitus, it is often regarded as the hepatic manifestation of the metabolic syndrome. No pharmacologic treatment has yet been proven for this disease. For most patients with presumed or confirmed NAFLD, the only proven strategy is to offer lifestyle advice that can lead to sustained weight loss. Since insulin resistance, oxidative stress, inflammation, and necro-apoptosis are involved in NAFLD pathogenesis, it seems that every potential therapeutic agent should target one or some of these pathologic events. There are many well known anti-oxidants, anti-inflammatory, and insulin sensitizer dietary supplements which have shown beneficial effects on NAFLD improvement in animal and human studies. The purpose of this review is to explore the existing evidences on dietary supplements considered to have hepatoprotective properties, and to present some proposed mechanisms by which they may protect against NAFLD.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Nonalcoholic fatty liver disease; Dietary supplementation; Treatment

**Core tip:** This review explores the existing evidences on dietary supplements considered to have anti-oxidant, anti-inflammatory, and/or insulin sensitizer properties, and their role in management of nonalcoholic fatty liver disease while addressing some of their proposed mechanism of action.

Eslamparast T, Eghtesad S, Poustchi H, Hekmatdoost A. Recent advances in dietary supplementation, in treating non-alcoholic fatty liver disease. *World J Hepatol* 2014; In press

**INTRODUCTION**

Non-alcoholic fatty liver disease (NAFLD) encompasses a range of conditions caused by fatty infiltration of the hepatocytes without significant amounts of alcohol use, that can be originated from multiple factors[[1](#_ENREF_1)]. NAFLD begins with simple hepatocyte steatosis, and progresses to nonalcoholic steatohepatitis (NASH), fibrosis of the hepatocytes, and liver cirrhosis, which can further progress to hepatocellular carcinoma (HCC)[[2](#_ENREF_2)]. Patients with NAFLD are usually asymptomatic and are diagnosed accidentally through routine checkup exams. Currently liver biopsies are considered gold standard for the diagnosis and staging of NASH, since there are no specific symptoms to differentiate between this disease and other liver disorders. Magnetic resonance spectroscopy (H1-MRS) and Fibroscan are noninvasive modalities for diagnosis and staging, assessing a larger section of the liver in comparison to liver biopsy[[3](#_ENREF_3),[4](#_ENREF_4)]. Other clinical diagnostic indices such as increased serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), as well as evidence of liver steatosis in ultrasonography are also routinely used[[5](#_ENREF_5)]. Developing effective therapies with minimal side-effects against NAFLD is critical for controlling the progression of this disease to end-stage liver disorders[[6](#_ENREF_6)].

**EPIDEMIOLOGY**

NAFLD is the most common diagnosis in subjects with altered aminotransferases in the Western world[[7](#_ENREF_7)], where one third of the population is affected[[8](#_ENREF_8)]. In Asia, recent reports showed a similar prevalence of NAFLD[[9](#_ENREF_9),[10](#_ENREF_10)]. About 20%-25% of adults with NASH have been reported to develop liver cirrhosis[[11](#_ENREF_11)]. About 30% to 40% of patients who develop cirrhosis secondary to NAFLD, will die of liver-related problems[[12](#_ENREF_12)]. The prevalence of NAFLD is different among men and women, and it increases with age, occurring in less than 20% of individuals younger than 20 years of age, and in more than 40% of those over the age of 60[[13](#_ENREF_13)]. NAFLD has also been identified in the pediatric population, prevailing at 2.6%, although it is estimated that its prevalence will increase to 22.5%-58.5% in obese children[[14](#_ENREF_14)]. Parallel to the rising prevalence of conditions such as obesity and type 2 diabetes mellitus (T2DM), the rate and prevalence of NAFLD is also increasing[[15](#_ENREF_15)]. NAFLD affects 40%-75% of patients with T2DM, 33%-76% of obese and 90% of morbidly obese people[[16](#_ENREF_16)].

**PATHOGENESIS**

The pathogenesis of NAFLD is complicated and while its exact mechanism remains largely unknown, different genetic factors and/or environmental elements seem to influence it[[12](#_ENREF_12),[17](#_ENREF_17)]. The “two-hit hypothesis” of NASH, originally explained by Day and James suggests that lipid deposition in the liver (first hit) is followed by a series of other, oxidative and hepatotoxic processes (second hit), caused by a mechanism currently not known[[18](#_ENREF_18)]. Several factors such as genetics, epigenetic mechanisms, as well as environmental elements, appear to promote hepatocyte fat deposition and insulin resistance, both of which further lead to the secondary pathologic events[[19](#_ENREF_19)], such as oxidative stress, lipid peroxidation, increased inflammatory responses, hepatic fibrosis and apoptosis[[20](#_ENREF_20)]. Other triggers such as lipotoxicity, endotoxemia, and adipocytokines or other inflammatory signals released from fat-infiltrated hepatocytes and adipose tissue, may promote oxidative stress in the liver, inducing the progression of NAFLD to NASH [[21](#_ENREF_21),[22](#_ENREF_22)].

**MANAGEMENT OF NAFLD**

Currently, the only proven strategy for NAFLD management is lifestyle modification techniques such as weight loss through diet and exercise. Since obesity strongly influences the development of NAFLD, weight loss is again the main objective in NAFLD management, and the first-line therapy. All NAFLD patients are encouraged to follow a low caloric diet, increase their physical activity, and stop smoking (if applicable)[[11](#_ENREF_11),[23](#_ENREF_23),[24](#_ENREF_24)]. Moreover, a wide range of drugs and supplements, including antioxidants, anti-inflammations, insulin sensitizers, and lipid lowering agents, have been evaluated in patients and experimental models of NAFLD, however none of them have shown long term efficacy[[25](#_ENREF_25),[26](#_ENREF_26)].

In the recent years, however, the beneficial effects of dietary supplements on NAFLD progression have received increasing attention since these substances have several advantages such as being widely available, while having low or minimal side effects[[27](#_ENREF_27)]. In the present review, we mainly focus on the recent advances of dietary supplements in NAFLD amelioration.

**RECENT FINDINGS FROM DIETARY SUPPLEMENTATION IN THE TREATMENT** **OF NAFLD**

***Antioxidants agents***

**Vitamin E and vitamin C:** Since oxidative stress is one of the factors involved in the pathogenesis of NAFLD, it was thought that antioxidant agents could be beneficial in its treatment. Thus, many clinical trials have evaluated the effects of vitamin E and/or vitamin C, as the main dietary sources of anti-oxidants to treat NAFLD. Nobili *et al*[28] have shown that vitamin E supplementation does not provide a greater benefit for NAFLD treatment, than diet and physical exercise[[28](#_ENREF_28)]. Akcam *et al*[[29](#_ENREF_29)] have reported that metformin is more efficacious in reducing metabolic parameters such as insulin resistance, fasting insulin and lipid levels, than dietary advice and vitamin E use in obese patients with NAFLD. A clinical trial using atorvastatin and vitamins E+C *vs* placebo, showed improved hepatic steatosis on computed tomography scans. It was not however detected whether this improvement was due to the combination treatment or a single compound alone[[30](#_ENREF_30)]. The TONIC randomized controlled trial showed that neither vitamin E nor metformin are superior to placebo in sustaining a reduction in ALT levels of pediatric NAFLD patients[[31](#_ENREF_31)]. A recent review article concluded that vitamin E is only recommended in adults with NASH who do not have diabetes or cirrhosis, or an aggressive histology[[32](#_ENREF_32)]. In a meta-analysis, adjuvant vitamin E was not shown to have a significant effect on normalizing serum ALT levels. Using higher doses of vitamin E, a longer duration of therapy or adding vitamin C did not alter the effect of these antioxidants on the measured outcomes either[[33](#_ENREF_33)]. There seems to be lacking evidence on the long-term effects of vitamin E use on histological improvements of NAFLD patients, which calls for larger, well-designed randomized controlled trials (RCTs) with histological endpoints, to really determine the efficacy of its use.

**Resveratrol:** Resveratrol (3,5,4-trihydroxystilbene) is a natural phenol produced by certain plants and found in the skin of red grapes. Resveratrol has been widely accepted as a chemopreventive agent that exerts other positive health effects as well because of its ability to take part in many biological activities. Resveratrol is thought to have antioxidative, anti-inflammatory, anti-cancer, anti-obesity, anti-diabetic, and anti-aging properties. Its positive effects on animal NAFLD models have been shown in several studies. In different studies, Resveratrol decreased NAFLD severity in animal models in the following ways: through TNF-alpha inhibition and antioxidant activities[[34](#_ENREF_34)], through the activation of AMPK[[35](#_ENREF_35),[36](#_ENREF_36)], by induction of skeletal muscle SIRT1 and SIRT4 expression[[37](#_ENREF_37)], by increasing the number of mitochondria, and specially, by increasing hepatic uncoupling protein 2 expression[[38](#_ENREF_38)], decreasing hepatic LDL receptor and SR-BI mRNA and protein expressions[[39](#_ENREF_39)], and the reduction of nuclear factor-kappaB (NF-kappaB) activity[[40](#_ENREF_40)].

Clinical trials evaluating the effects of Resveratrol supplementation on NAFLD characteristics are scarce. A recent study, administering Resveratrol vs. placebo for eight weeks, not only failed to show any significantly improvements in any NAFLD features in the Resveratrol group, it also showed an increase in hepatic stress, based on increased liver enzyme levels[[41](#_ENREF_41)]. A different trial however, did find a significant improvement in NAFLD characteristics after 12 wk of supplementation with 500mg Resveratrol[[42](#_ENREF_42)]. It appears that the dose and duration of Resveratrol administration is important in its efficacy. Future clinical studies with different dosages and durations are needed to clarify the true impact of Resveratrol treatment in NAFLD/NASH patients [[43](#_ENREF_43)].

**Anthocyanin:** Anthocyanins (ACNs) are water-soluble bioactive compounds of the polyphenol class that are present in many plant based products. It has been reported that ACNs decrease hepatic lipid accumulation and may counteract oxidative stress and hepatic inflammation in animal studies, but their benefits in patients with NAFLD has not yet been well elucidated[[44](#_ENREF_44)]. There is only one study evaluating the effects of ACN on NAFLD patients; Suda *et al*[45] have reported that supplementation with 400mg of acylated ACNs could reduce levels of liver enzymes, in particular gamma-glutamyl transferases in patients with NAFLD. This clinical trial had many limitations; liver damage was not directly assessed, fatty liver was not confirmed by direct imaging, and the effect of acylated ACNs was not compared to that of a control food or to the lack of intervention[[45](#_ENREF_45)]. More research studies are therefore required to evaluate the effects of ACNs supplementation on NAFLD features.

**Green tea extract:** It has been shown that the main important green tea polyphenol, epigallocatechin-3-gallate (EGCG), has a positive therapeutic effect on obesity, features of metabolic syndrome, and liver steatosis in mice[[46](#_ENREF_46)]. In experimental models of NAFLD, EGCG supplementation significantly decreased weight gain, total and visceral body fat, insulin resistance, liver steatosis, serum cholesterol, and monocyte chemoattractant protein concentrations[[46](#_ENREF_46)].

Both *in vitro* and *in vivo* experiments have revealed that green tea and EGCG could prevent steatosis by reducing dietary absorption of lipids and carbohydrates, and by the inhibition of adipose tissue breakdown, and *de novo* lipogenesis in both hepatic and adipose tissues, through the stimulation of β-oxidation and thermogenesis in the liver, and by improving insulin sensitivity. Furthermore, EGCG may inhibit the development of steatohepatitis from fatty liver disease, through its antioxidant and anti-inflammatory characteristics[[47](#_ENREF_47)]. Currently, there are no randomized, controlled trials in humans, evaluating the effects of green tea on NAFLD. These studies are needed to provide enough evidence that green tea can effectively prevent the development and/or progression of NAFLD[[48](#_ENREF_48)].

**Coffee:** Both epidemiological and animal studies have shown that drinking coffee on a regular basis can decrease the risk of T2DM development[[49-51](#_ENREF_49)]. A recent case-control study comparing coffee vs. non-coffee drinkers showed that fatty liver occurred less frequently in coffee drinkers, and that drinking coffee was inversely associated with the degree of liver brightness, as well as obesity and insulin resistance[[52](#_ENREF_52)]. Among NASH patients, coffee consumption has been shown to be significantly associated with a reduced risk of fibrosis[[53](#_ENREF_53)].

More research is needed to determine the protective properties of caffeine against NAFLD. Coffee contains certain phytochemicals with potential antioxidant properties, which may be protective against cardiovascular and liver diseases, and malignancies. The anti-oxidative, anti-inflammatory, and anti-fibrotic properties of coffee might explain its hepatoprotective effects in NAFLD[[54](#_ENREF_54),[55](#_ENREF_55)].

**Garlic:** Garlic-derived S-allylmercaptocysteine (SAMC) has a therapeutic role in diabetes and nonalcoholic fatty liver disease due to its properties in the regulation of lipogenesis and glucose metabolism[[56](#_ENREF_56)]. Results of two studies show that SAMC decreases the liver injury caused by NAFLD, while decreasing fat build-up, and collagen formation. This may occur because SAMC takes part in different activities at the molecular level that affect NAFLD, by for example decreasing lipogenesis and restoring lipolysis markers. The expression of pro-fibrogenic factors is also reduced by SAMC, as well as oxidative stress in the liver, by means of cytochrome P450 2E1-dependent pathway inhibition. SAMC may partially prevent NAFLD-induced inflammation as well, by reducing pro-inflammatory mediators, chemokines and suppressor of cytokine signaling. The protective effects of SAMC are also partly shown through its ability to restore the altered phosphorylation status of FFAs-dependent MAP kinase pathways, and to diminish the activity of nuclear transcription factors such as NF-kappaB and AP-1, while reducing apoptosis and enhancing autophagy during NAFLD development[[57](#_ENREF_57),[58](#_ENREF_58)].

In addition, garlic essential oil (GEO) and its major organosulfur component diallyl disulfide (DADS), also have therapeutic effects on the development of NAFLD. They exert anti-obesity and anti-hyperlipidemic effects by reducing weight gain, adipose tissue weight, and serum lipid parameters. They significantly decrease the release of pro-inflammatory cytokines in the serum, while at the same time elevating in the hepatic antioxidant capacity by inhibiting cytochrome P450 2E1 expression during NAFLD development. The anti-NAFLD effects of GEO and DADS are mediated through the down-regulation of sterol regulatory element binding protein-1c, acetyl-CoA carboxylase, fatty acid synthase, and 3-hydroxy-3-methylglutaryl-coenzyme[[59](#_ENREF_59)]. Clinical trials are needed to confirm these experimental studies.

**Ginger:** Several mechanisms have been proposed by which ginger may prevent NAFLD or slow its progression to other liver diseases, such as increasing insulin sensitivity, inducing the activation of peroxisome proliferator-activated receptor gamma, which in turn induces adiponectin and down-regulates pro-inflammatory cytokines, changing the balance between adiponectin and tumor necrosis factor-alpha in favor of adiponectin, promoting considerable antioxidant effects and antidyslipidemic properties, and reducing hepatic triglyceride content which can prevent steatosis. These mechanisms indicate that ginger possesses interesting potentials for serving as a natural supplement for the prevention and treatment of NAFLD[[60](#_ENREF_60)]. It might suppress fructose-stimulated overexpression of carbohydrate response element-binding protein (ChREBP) at the mRNA and protein levels in hepatocytes, which results in down regulation of the ChREBP-targeted lipogenic genes responsible for fatty acid biosynthesis, while expression of neither peroxisome proliferator-activated receptor- (PPAR-) alpha and its downstream genes, nor PPAR-gamma and sterol regulatory element-binding protein 1c is altered[[61](#_ENREF_61)]. Randomized clinical trials are needed to confirm these effects in patients with NAFLD.

***Anti-inflammatory agents***

**Polyunsaturated fatty acids and monounsaturated fatty acids supplementation:** Polyunsaturated fatty acids (PUFAs), especially n-3 PUFAs, are used to promote weight loss, and to reduce hepatic triglyceride accumulation, while improving insulin sensitivity and reducing steatosis, and hepatic damage in patients with NAFLD[[62-64](#_ENREF_62)]. They are also thought to exert anti-inflammatory effects[[65](#_ENREF_65)]. N-3 fatty acids affect lipid metabolism by mediating genomic pathways and regulating the transcription of genes involved in lipid metabolism[[66](#_ENREF_66)]. They improve insulin sensitivity by decreasing hepatic TNFα expression, repress fatty acid synthesis by negatively controlling sterol regulatory element binding protein-1c (SREBP-1c), and enhance fatty acid oxidation by positively controlling peroxisome proliferator-activated receptor-α (PPARα)[[67](#_ENREF_67),[68](#_ENREF_68)]. Several studies support the protective effects of n-3 PUFAs in NAFLD. Among these, Capanni *et al*[[69](#_ENREF_69)] investigated the effects of n-3 PUFA supplementation (1 g/d for 12 mo) in 56 NAFLD patients. Their results indicated that n-3 PUFAs improved NAFLD characteristics such as ALT, AST, GGT, triglyceride and fasting glucose concentrations. Another clinical trial conducted in 23 patients with NASH found the same results[[70](#_ENREF_70)]. A recent systematic review reported a beneficial effect of omega-3 supplementation on hepatic fat content and AST, although the effect size was relatively small[[71](#_ENREF_71)]. The optimal dose and duration of this therapy need to be addressed in larger clinical trials in the future. Data on omega-6 fatty acids are very limited and mainly restricted to animal models.

Moreover, dietary monounsaturated fatty acids (MUFAs) may prevent the development of NAFLD by reducing the oxidization of low-density lipoprotein (LDL), serum concentrations of LDL and total cholesterol (TC) and triacylglycerols, while decreasing body fat accumulation and postprandial adiponectin expression. It is shown that the replacing dietary carbohydrate and saturated fat consumption with MUFAs, reduces the blood pressure and glucose concentrations, and increases serum high-density lipoprotein (HDL) levels[[72](#_ENREF_72)]. The probable mechanisms for the beneficial effects of MUFA on liver fat content may be related to their roles in the regulation of insulin sensitizing gene expression[[7](#_ENREF_7)], and in the reduction of inflammation[[73](#_ENREF_73)], as well as to their inhibitory effects on nuclear factor- κB (NF-κB)[[74](#_ENREF_74)]. In a study, MUFA decreased the expression of hepatic lipogenesis and gluconeogenesis genes and SREBP in fatty rats[[75](#_ENREF_75)]. Further investigations are warranted to ascertain the role of MUFA on NAFLD.

**Vitamin D:** Evidence supporting the immunoregulatory roles of vitamin D continues to increase. Recent studies have indicated that deficiencies in vitamin D can result in insulin resistance, metabolic syndrome, and NAFLD[[76](#_ENREF_76)]. In one study, rats who were fed a western diet along with vitamin D depletion had significantly more steatosis, lobular inﬂammation, and NAFLD activity scores in comparison to animals with sufficient vitamin D intakes[[77](#_ENREF_77)]. In humans, vitamin D deficiency has been correlated with a more severe NAFLD activity score and hepatic fibrosis[[78](#_ENREF_78)], perhaps owing to the greater oxidative stress resulting from vitamin D deficiency [[79](#_ENREF_79)]. Hepatic expression of vitamin D receptors, CYP2R1 and CYP 27A1, negatively correlates with the severity of steatosis, inflammation, and NAFLD scores in patients with this disease[[80](#_ENREF_80)]. A recent study found a significant association between NAFLD and low serum vitamin D levels[[81](#_ENREF_81)]; this relationship remained significant even after adjustments were made for the presence of other metabolic syndrome features. Evidence from liver biopsies have shown that serum vitamin D levels are significantly related with the stage of hepatic fibrosis[[82](#_ENREF_82)]. Clinical trials have not yet been published to evaluate the effect of vitamin D supplementation on NAFLD characteristics.

**Probiotics, prebiotics and symbiotic:** It is known that the liver is susceptible to the exposure of intestine-derived bacterial products because of a close anatomic and functional connection between the intestinal lumen and the liver through the portal system[[83](#_ENREF_83),[84](#_ENREF_84)]. The gut-liver axis is an important pathway in NAFLD development, which is associated with small intestinal bacterial overgrowth and increased intestinal permeability[[85](#_ENREF_85),[86](#_ENREF_86)]. The contribution of microflora in NAFLD progression is mainly based on increased oxidative stress in the liver, which is caused by the increased ethanol and lipopolysaccharide production in the intestine, further causing the release of inflammatory cytokines [[87](#_ENREF_87),[88](#_ENREF_88)].

Probiotics are live microorganisms that are beneficial to human health when ingested[[88](#_ENREF_88)]. The therapeutic effects of probiotics have been demonstrated in several animal models of NAFLD[[86](#_ENREF_86),[89-91](#_ENREF_89)]; however clinical trials are scarce[[92-95](#_ENREF_92)]. In a recent double blind, placebo controlled, clinical trial, we found that 28 wk of synbiotic supplementation can significantly decrease liver enzymes, inflammatory cytokines, NF-kB activity, and fibrosis scores so that this supplementation in addition to lifestyle modification was significantly superior to lifestyle modification alone; whether these effects will sustain with longer treatment durations remains to be determined[[89](#_ENREF_89)].

***Insulin sensitizers and lipid lowering agents***

**Cinnamon:** Cinnamon might play a potential role in the reduction of post-prandial intestinal glucose absorption through the inhibition of pancreatic enzymes such as α-amylase and α-glucosidase, and by stimulating cellular glucose uptake by membrane translocation of glucose transporter-4, which stimulates insulin release, glucose metabolism, glycogen synthesis, and inhibits gluconeogenesis. These actions may ameliorate fasting blood glucose, LDL, and hemoglobin A1c, and might increase HDL cholesterol and insulin concentrations[[96](#_ENREF_96)].

Since one of the most important therapeutic strategies for NAFLD is modulating insulin resistance and oxidative stress, we thought that cinnamon could have beneficial effects on NAFLD features too. Thus, we investigated this hypothesis in a double-blind, placebo-controlled trial, and found that 12 wk of cinnamon supplementation significantly decreases HOMA (Homeostatic Model Assessment) index, FBS (fasting blood glucose), total cholesterol, triglyceride, liver enzymes, and high-sensitivity C-reactive protein in patients with NAFLD, however we did not find any significant changes in serum HDL levels[[97](#_ENREF_97)]. Further clinical trials of longer durations are recommended to elucidate the exact effects of cinnamon on NAFLD characteristics.

**Curcumin:** It has shown that curcumin can reduce serum lipid levels, and liver steatosis. Furthermore, it may prevent fatty liver progression to steatohepatitis due to its potent antioxidant and anti-inflammatory activities[[98](#_ENREF_98),[99](#_ENREF_99)]. Curcumin can reduce the expression of lipogenic genes in the liver and inflammatory responses of adipose tissue[[100](#_ENREF_100)], while enhancing the antioxidant defense system, attenuating mitochondrial dysfunction and inhibiting apoptosis[[101](#_ENREF_101),[102](#_ENREF_102)]. We did not find any clinical trial evaluating the effect of curcumin in patients with NAFLD.

**Quercetine:** Quercetin, a plant-derived bioflavonoid, has been reported to provide an improved health status to its consumers, particularly with regard to obesity and diabetes[[103](#_ENREF_103)]. Studies have demonstrated that quercetin can modestly reduce weight and regulate the expression of genes related to *in vitro* adipogenesis[[103](#_ENREF_103),[104](#_ENREF_104)]. Quercetin reduces inflammatory cytokine levels and improves lipid peroxidation and insulin resistance in animal models of NAFLD, and its beneficial effects are dose dependent[[103](#_ENREF_103),[105](#_ENREF_105)]. There is no clinical trial evaluating its effects on patients with NAFLD.

**Carnitin:** Carnitine is an essential component of mitochondrial beta oxidation. It takes part in the transportation of long-chain fatty acids into the mitochondria. Abnormalities in the mitochondria have been found to play an important role in NAFLD and NASH development. There are two published clinical trials evaluating the effects of carnitin supplementation on NAFLD characteristics. Lim *et al*[106] showed that 3 mo of carnitine supplementation improved NAFLD features by improving serum liver function tests and mitochondrial DNA copies[[106](#_ENREF_106)]. Malaguarnera *et al*[107] showed that the addition of an L-carnitine supplement to an individual’s diet for 24 wk, reduced TNF-α and CRP, and improved liver function, plasma glucose levels, lipid profile, HOMA-IR, and histological manifestations of NASH[[107](#_ENREF_107)]; how long these effects will sustain was not evaluated.

**CONCLUSION**

Since there is no proven pharmacologic treatment for NAFLD, it is critically important to find dietary approaches to the prevention, attenuation, or reversal of hepatic steatosis, and its progression to steatohepatitis. As insulin resistance, oxidative stress, and inflammation are involved in pathogenesis of NAFLD, it seems that dietary supplements that can modulate these pathologies could be useful in the treatment of NAFLD. These supplements have shown beneficial effects in animal models of NAFLD, however clinical trials are scarce. Further clinical trials are needed to support the use of supplements, either as preventative or therapeutic agents that effectively prevent the development and/or worsening of liver steatosis in patients with NAFLD.

**REFERENCES**

1 **McCullough AJ**. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. *Clin Liver Dis* 2004; **8**: 521-533, viii [PMID: 15331061 DOI: 10.1016/j.cld.2004.04.004]

2 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121 [PMID: 16012941 DOI: 10.1053/j.gastro.2005.04.014]

3 **Malekzadeh R**, Poustchi H. Fibroscan for assessing liver fibrosis: An acceptable alternative for liver biopsy: Fibroscan: an acceptable alternative for liver biopsy. *Hepat Mon* 2011; **11**: 157-158 [PMID: 22087136]

4 **Fierbinteanu-Braticevici C**, Dina I, Petrisor A, Tribus L, Negreanu L, Carstoiu C. Noninvasive investigations for non alcoholic fatty liver disease and liver fibrosis. *World J Gastroenterol* 2010; **16**: 4784-4791 [PMID: 20939106 DOI: 10.3748/wjg.v16.i38.4784]

5 **Adams LA**, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005; **42**: 132-138 [PMID: 15629518 DOI: 10.1016/j.jhep.2004.09.012]

6 **Stickel F**, Hellerbrand C. Non-alcoholic fatty liver disease as a risk factor for hepatocellular carcinoma: mechanisms and implications. *Gut* 2010; **59**: 1303-1307 [PMID: 20650925 DOI: 10.1136/gut.2009.199661]

7 **Clark SJ**, Shojaee-Moradie F, Croos P, Seed PT, Umpleby AM, Wendon JA, Miell J. Temporal changes in insulin sensitivity following the development of acute liver failure secondary to acetaminophen. *Hepatology* 2001; **34**: 109-115 [PMID: 11431740 DOI: 10.1053/jhep.2001.25514]

8 **Vernon G**, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; **34**: 274-285 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]

9 **Eguchi Y**, Hyogo H, Ono M, Mizuta T, Ono N, Fujimoto K, Chayama K, Saibara T. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. *J Gastroenterol* 2012; **47**: 586-595 [PMID: 22328022 DOI: 10.1007/s00535-012-0533-z]

10 **Farrell GC**, Wong VW, Chitturi S. NAFLD in Asia--as common and important as in the West. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 307-318 [PMID: 23458891 DOI: 10.1038/nrgastro.2013.34]

11 **Ratziu V**, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010; **53**: 372-384 [PMID: 20494470 DOI: 10.1016/j.jhep.2010.04.008]

12 **McCullough AJ**. Pathophysiology of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2006; **40** Suppl 1: S17-S29 [PMID: 16540762]

13 **Dowman JK**, Tomlinson JW, Newsome PN. Systematic review: the diagnosis and staging of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2011; **33**: 525-540 [PMID: 21198708 DOI: 10.1111/j.1365-2036.2010.04556.x]

14 **Tarantino G**, Saldalamacchia G, Conca P, Arena A. Non-alcoholic fatty liver disease: further expression of the metabolic syndrome. *J Gastroenterol Hepatol* 2007; **22**: 293-303 [PMID: 17295757 DOI: 10.1111/j.1440-1746.2007.04824.x]

15 **Gastaldelli A**, Cusi K, Pettiti M, Hardies J, Miyazaki Y, Berria R, Buzzigoli E, Sironi AM, Cersosimo E, Ferrannini E, Defronzo RA. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. *Gastroenterology* 2007; **133**: 496-506 [PMID: 17681171 DOI: 10.1053/j.gastro.2007.04.068]

16 **Lazo M**, Clark JM. The epidemiology of nonalcoholic fatty liver disease: a global perspective. *Semin Liver Dis* 2008; **28**: 339-350 [PMID: 18956290]

17 **Cohen JC**, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science* 2011; **332**: 1519-1523 [PMID: 21700865 DOI: 10.1126/science.1204265]

18 **Day CP**, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology* 1998; **114**: 842-845 [PMID: 9547102 DOI: 10.1016/S0016-5085(98)70599-2]

19 **Day CP**. Genetic and environmental susceptibility to non-alcoholic fatty liver disease. *Dig Dis* 2010; **28**: 255-260 [PMID: 20460920 DOI: 10.1159/000282098]

20 **Polyzos SA**, Kountouras J, Zavos Ch. The multi-hit process and the antagonistic roles of tumor necrosis factor-alpha and adiponectin in non alcoholic fatty liver disease. *Hippokratia* 2009; **13**: 127; author reply 128 [PMID: 19561788]

21 **Polyzos SA**, Kountouras J, Zavos C, Deretzi G. Nonalcoholic fatty liver disease: multimodal treatment options for a pathogenetically multiple-hit disease. *J Clin Gastroenterol* 2012; **46**: 272-284 [PMID: 22395062 DOI: 10.1097/MCG.0b013e31824587e0]

22 **Giby VG**, Ajith TA. Role of adipokines and peroxisome proliferator-activated receptors in nonalcoholic fatty liver disease. *World J Hepatol* 2014; **6**: 570-579 [PMID: 25232450 DOI: 10.4254/wjh.v6.i8.570]

23 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**: 2005-2023 [PMID: 22488764 DOI: 10.1002/hep.25762]

24 **Nascimbeni F**, Pais R, Bellentani S, Day CP, Ratziu V, Loria P, Lonardo A. From NAFLD in clinical practice to answers from guidelines. *J Hepatol* 2013; **59**: 859-871 [PMID: 23751754 DOI: 10.1016/j.jhep.2013.05.044]

25 **Gossard AA**, Lindor KD. Current therapies for nonalcoholic fatty liver disease. *Drugs Today (Barc)* 2011; **47**: 915-922 [PMID: 22348916 DOI: 10.1358/dot.2011.47.12.1688530]

26 **Keating SE**, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **57**: 157-166 [PMID: 22414768 DOI: 10.1016/j.jhep.2012.02.023]

27 **Firenzuoli F**, Gori L. Herbal medicine today: clinical and research issues. *Evid Based Complement Alternat Med* 2007; **4**: 37-40 [PMID: 18227931 DOI: 10.1093/ecam/nem096]

28 **Nobili V**, Manco M, Devito R, Ciampalini P, Piemonte F, Marcellini M. Effect of vitamin E on aminotransferase levels and insulin resistance in children with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2006; **24**: 1553-1561 [PMID: 17206944 DOI: 10.1111/j.1365-2036.2006.03161.x]

29 **Akcam M**, Boyaci A, Pirgon O, Kaya S, Uysal S, Dundar BN. Therapeutic effect of metformin and vitamin E versus prescriptive diet in obese adolescents with fatty liver. *Int J Vitam Nutr Res* 2011; **81**: 398-406 [PMID: 22673924 DOI: 10.1024/0300-9831/a000086]

30 **Arendt BM**, Allard JP. Effect of atorvastatin, vitamin E and C on nonalcoholic fatty liver disease: is the combination required? *Am J Gastroenterol* 2011; **106**: 78-80 [PMID: 21212755 DOI: 10.1038/ajg.2010.310]

31 **Lavine JE**, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, Abrams SH, Scheimann AO, Sanyal AJ, Chalasani N, Tonascia J, Ünalp A, Clark JM, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA* 2011; **305**: 1659-1668 [PMID: 21521847 DOI: 10.1001/jama.2011.520]

32 **Pacana T**, Sanyal AJ. Vitamin E and nonalcoholic fatty liver disease. *Curr Opin Clin Nutr Metab Care* 2012; **15**: 641-648 [PMID: 23075940 DOI: 10.1097/MCO.0b013e328357f747]

33 **Sarkhy AA**, Al-Hussaini AA, Nobili V. Does vitamin E improve the outcomes of pediatric nonalcoholic fatty liver disease? A systematic review and meta-analysis. *Saudi J Gastroenterol* 2014; **20**: 143-153 [PMID: 24976277 DOI: 10.4103/1319-3767.132983]

34 **Bujanda L**, Hijona E, Larzabal M, Beraza M, Aldazabal P, García-Urkia N, Sarasqueta C, Cosme A, Irastorza B, González A, Arenas JI. Resveratrol inhibits nonalcoholic fatty liver disease in rats. *BMC Gastroenterol* 2008; **8**: 40 [PMID: 18782455 DOI: 10.1186/1471-230X-8-40]

35 **Shang J**, Chen LL, Xiao FX, Sun H, Ding HC, Xiao H. Resveratrol improves non-alcoholic fatty liver disease by activating AMP-activated protein kinase. *Acta Pharmacol Sin* 2008; **29**: 698-706 [PMID: 18501116 DOI: 10.1111/j.1745-7254.2008.00807.x]

36 **Choi YJ**, Suh HR, Yoon Y, Lee KJ, Kim DG, Kim S, Lee BH. Protective effect of resveratrol derivatives on high-fat diet induced fatty liver by activating AMP-activated protein kinase. *Arch Pharm Res* 2014; **37**: 1169-1176 [PMID: 24633463 DOI: 10.1007/s12272-014-0347-z]

37 **Tauriainen E**, Luostarinen M, Martonen E, Finckenberg P, Kovalainen M, Huotari A, Herzig KH, Lecklin A, Mervaala E. Distinct effects of calorie restriction and resveratrol on diet-induced obesity and Fatty liver formation. *J Nutr Metab* 2011; **2011**: 525094 [PMID: 21977315 DOI: 10.1155/2011/525094]

38 **Poulsen MM**, Larsen JØ, Hamilton-Dutoit S, Clasen BF, Jessen N, Paulsen SK, Kjær TN, Richelsen B, Pedersen SB. Resveratrol up-regulates hepatic uncoupling protein 2 and prevents development of nonalcoholic fatty liver disease in rats fed a high-fat diet. *Nutr Res* 2012; **32**: 701-708 [PMID: 23084643 DOI: 10.1016/j.nutres.2012.08.004]

39 **Xin P**, Han H, Gao D, Cui W, Yang X, Ying C, Sun X, Hao L. Alleviative effects of resveratrol on nonalcoholic fatty liver disease are associated with up regulation of hepatic low density lipoprotein receptor and scavenger receptor class B type I gene expressions in rats. *Food Chem Toxicol* 2013; **52**: 12-18 [PMID: 23127599 DOI: 10.1016/j.fct.2012.10.026]

40 **Li L**, Hai J, Li Z, Zhang Y, Peng H, Li K, Weng X. Resveratrol modulates autophagy and NF-κB activity in a murine model for treating non-alcoholic fatty liver disease. *Food Chem Toxicol* 2014; **63**: 166-173 [PMID: 23978414 DOI: 10.1016/j.fct.2013.08.036]

41 **Chachay VS**, Macdonald GA, Martin JH, Whitehead JP, O'Moore-Sullivan TM, Lee P, Franklin M, Klein K, Taylor PJ, Ferguson M, Coombes JS, Thomas GP, Cowin GJ, Kirkpatrick CM, Prins JB, Hickman IJ. Resveratrol Does Not Benefit Patients With Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2014 [PMID: 24582567 DOI: 10.1016/j.cgh.2014.02.024]

42 **Faghihzadeh F,** Adibi P, Rafiei R, Hekmatdoost A. Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease. *Nutr Res* 2014; In press [PMID: 25311610 DOI: 10.1016/j.nutres.2014.09.005]

43 **Heebøll S**, Thomsen KL, Pedersen SB, Vilstrup H, George J, Grønbæk H. Effects of resveratrol in experimental and clinical non-alcoholic fatty liver disease. *World J Hepatol* 2014; **6**: 188-198 [PMID: 24799987 DOI: 10.4254/wjh.v6.i4.188]

44 **Valenti L**, Riso P, Mazzocchi A, Porrini M, Fargion S, Agostoni C. Dietary anthocyanins as nutritional therapy for nonalcoholic fatty liver disease. *Oxid Med Cell Longev* 2013; **2013**: 145421 [PMID: 24282628 DOI: 10.1155/2013/145421]

45 **Suda I**, Ishikawa F, Hatakeyama M, Miyawaki M, Kudo T, Hirano K, Ito A, Yamakawa O, Horiuchi S. Intake of purple sweet potato beverage affects on serum hepatic biomarker levels of healthy adult men with borderline hepatitis. *Eur J Clin Nutr* 2008; **62**: 60-67 [PMID: 17299464 DOI: 10.1038/sj.ejcn.1602674]

46 **Bose M**, Lambert JD, Ju J, Reuhl KR, Shapses SA, Yang CS. The major green tea polyphenol, (-)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. *J Nutr* 2008; **138**: 1677-1683 [PMID: 18716169]

47 **Xiao J**, Ho CT, Liong EC, Nanji AA, Leung TM, Lau TY, Fung ML, Tipoe GL. Epigallocatechin gallate attenuates fibrosis, oxidative stress, and inflammation in non-alcoholic fatty liver disease rat model through TGF/SMAD, PI3 K/Akt/FoxO1, and NF-kappa B pathways. *Eur J Nutr* 2014; **53**: 187-199 [PMID: 23515587 DOI: 10.1007/s00394-013-0516-8]

48 **Masterjohn C**, Bruno RS. Therapeutic potential of green tea in nonalcoholic fatty liver disease. *Nutr Rev* 2012; **70**: 41-56 [PMID: 22221215 DOI: 10.1111/j.1753-4887.2011.00440.x]

49 **Birerdinc A**, Stepanova M, Pawloski L, Younossi ZM. Caffeine is protective in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2012; **35**: 76-82 [PMID: 22059453 DOI: 10.1111/j.1365-2036.2011.04916.x]

50 **Yamauchi R**, Kobayashi M, Matsuda Y, Ojika M, Shigeoka S, Yamamoto Y, Tou Y, Inoue T, Katagiri T, Murai A, Horio F. Coffee and caffeine ameliorate hyperglycemia, fatty liver, and inflammatory adipocytokine expression in spontaneously diabetic KK-Ay mice. *J Agric Food Chem* 2010; **58**: 5597-5603 [PMID: 20405946 DOI: 10.1021/jf904062c]

51 **Yesil A**, Yilmaz Y. Review article: coffee consumption, the metabolic syndrome and non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2013; **38**: 1038-1044 [PMID: 24024834 DOI: 10.1111/apt.12489]

52 **Catalano D**, Martines GF, Tonzuso A, Pirri C, Trovato FM, Trovato GM. Protective role of coffee in non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci* 2010; **55**: 3200-3206 [PMID: 20165979 DOI: 10.1007/s10620-010-1143-3]

53 **Molloy JW**, Calcagno CJ, Williams CD, Jones FJ, Torres DM, Harrison SA. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology* 2012; **55**: 429-436 [PMID: 21987293 DOI: 10.1002/hep.24731]

54 **Chen S**, Teoh NC, Chitturi S, Farrell GC. Coffee and non-alcoholic fatty liver disease: brewing evidence for hepatoprotection? *J Gastroenterol Hepatol* 2014; **29**: 435-441 [PMID: 24199670 DOI: 10.1111/jgh.12422]

55 **Salomone F**, Li Volti G, Vitaglione P, Morisco F, Fogliano V, Zappalà A, Palmigiano A, Garozzo D, Caporaso N, D'Argenio G, Galvano F. Coffee enhances the expression of chaperones and antioxidant proteins in rats with nonalcoholic fatty liver disease. *Transl Res* 2014; **163**: 593-602 [PMID: 24365744 DOI: 10.1016/j.trsl.2013.12.001]

56 **Takemura S**, Minamiyama Y, Kodai S, Shinkawa H, Tsukioka T, Okada S, Azuma H, Kubo S. S-Allyl cysteine improves nonalcoholic fatty liver disease in type 2 diabetes Otsuka Long-Evans Tokushima Fatty rats via regulation of hepatic lipogenesis and glucose metabolism. *J Clin Biochem Nutr* 2013; **53**: 94-101 [PMID: 24062606 DOI: 10.3164/jcbn.13-1]

57 **Xiao J**, Guo R, Fung ML, Liong EC, Chang RC, Ching YP, Tipoe GL. Garlic-Derived S-Allylmercaptocysteine Ameliorates Nonalcoholic Fatty Liver Disease in a Rat Model through Inhibition of Apoptosis and Enhancing Autophagy. *Evid Based Complement Alternat Med* 2013; **2013**: 642920 [PMID: 23861709 DOI: 10.1155/2013/642920]

58 **Xiao J**, Ching YP, Liong EC, Nanji AA, Fung ML, Tipoe GL. Garlic-derived S-allylmercaptocysteine is a hepato-protective agent in non-alcoholic fatty liver disease in vivo animal model. *Eur J Nutr* 2013; **52**: 179-191 [PMID: 22278044 DOI: 10.1007/s00394-012-0301-0]

59 **Lai YS**, Chen WC, Ho CT, Lu KH, Lin SH, Tseng HC, Lin SY, Sheen LY. Garlic essential oil protects against obesity-triggered nonalcoholic fatty liver disease through modulation of lipid metabolism and oxidative stress. *J Agric Food Chem* 2014; **62**: 5897-5906 [PMID: 24857364 DOI: 10.1021/jf500803c]

60 **Sahebkar A**. Potential efficacy of ginger as a natural supplement for nonalcoholic fatty liver disease. *World J Gastroenterol* 2011; **17**: 271-272 [PMID: 21246004 DOI: 10.3748/wjg.v17.i2.271]

61 **Gao H**, Guan T, Li C, Zuo G, Yamahara J, Wang J, Li Y. Treatment with ginger ameliorates fructose-induced Fatty liver and hypertriglyceridemia in rats: modulation of the hepatic carbohydrate response element-binding protein-mediated pathway. *Evid Based Complement Alternat Med* 2012; **2012**: 570948 [PMID: 23193424 DOI: 10.1155/2012/570948]

62 **Masterton GS**, Plevris JN, Hayes PC. Review article: omega-3 fatty acids - a promising novel therapy for non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2010; **31**: 679-692 [PMID: 20415840 DOI: 10.1111/j.1365-2036.2009.04230.x]

63 **Storlien LH**, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG, Pascoe WS. Fish oil prevents insulin resistance induced by high-fat feeding in rats. *Science* 1987; **237**: 885-888 [PMID: 3303333 DOI: 10.1126/science.3303333]

64 **Levy JR**, Clore JN, Stevens W. Dietary n-3 polyunsaturated fatty acids decrease hepatic triglycerides in Fischer 344 rats. *Hepatology* 2004; **39**: 608-616 [PMID: 14999679 DOI: 10.1002/hep.20093]

65 **Mouzaki M**, Allard JP. The role of nutrients in the development, progression, and treatment of nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2012; **46**: 457-467 [PMID: 22469640 DOI: 10.1097/MCG.0b013e31824cf51e]

66 **Jump DB**. N-3 polyunsaturated fatty acid regulation of hepatic gene transcription. *Curr Opin Lipidol* 2008; **19**: 242-247 [PMID: 18460914 DOI: 10.1097/MOL.0b013e3282ffaf6a]

67 **Ghafoorunissa A**, Rajkumar L, Acharya V. Dietary (n-3) long chain polyunsaturated fatty acids prevent sucrose-induced insulin resistance in rats. *J Nutr* 2005; **135**: 2634-2638 [PMID: 16253960]

68 **Teran-Garcia M**, Adamson AW, Yu G, Rufo C, Suchankova G, Dreesen TD, Tekle M, Clarke SD, Gettys TW. Polyunsaturated fatty acid suppression of fatty acid synthase (FASN): evidence for dietary modulation of NF-Y binding to the Fasn promoter by SREBP-1c. *Biochem J* 2007; **402**: 591-600 [PMID: 17313375 DOI: 10.1042/BJ20061722]

69 **Capanni M**, Calella F, Biagini MR, Genise S, Raimondi L, Bedogni G, Svegliati-Baroni G, Sofi F, Milani S, Abbate R, Surrenti C, Casini A. Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: a pilot study. *Aliment Pharmacol Ther* 2006; **23**: 1143-1151 [PMID: 16611275 DOI: 10.1111/j.1365-2036.2006.02885.x]

70 **Tanaka N**, Sano K, Horiuchi A, Tanaka E, Kiyosawa K, Aoyama T. Highly purified eicosapentaenoic acid treatment improves nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2008; **42**: 413-418 [PMID: 18277895 DOI: 10.1097/MCG.0b013e31815591aa]

71 **Parker HM**, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **56**: 944-951 [PMID: 22023985 DOI: 10.1016/j.jhep.2011.08.018]

72 **Hâncu N**, Roman G, Nită C, Negrean M. Metabolic syndrome--practical approach. *Rom J Intern Med* 2004; **42**: 237-245 [PMID: 15529614]

73 **Serrano-Martinez M**, Palacios M, Martinez-Losa E, Lezaun R, Maravi C, Prado M, Martínez JA, Martinez-Gonzalez MA. A Mediterranean dietary style influences TNF-alpha and VCAM-1 coronary blood levels in unstable angina patients. *Eur J Nutr* 2005; **44**: 348-354 [PMID: 16151968 DOI: 10.1007/s00394-004-0532-9]

74 **Madigan C**, Ryan M, Owens D, Collins P, Tomkin GH. Dietary unsaturated fatty acids in type 2 diabetes: higher levels of postprandial lipoprotein on a linoleic acid-rich sunflower oil diet compared with an oleic acid-rich olive oil diet. *Diabetes Care* 2000; **23**: 1472-1477 [PMID: 11023139 DOI: 10.2337/diacare.23.10.1472]

75 **Sato K**, Arai H, Mizuno A, Fukaya M, Sato T, Koganei M, Sasaki H, Yamamoto H, Taketani Y, Doi T, Takeda E. Dietary palatinose and oleic acid ameliorate disorders of glucose and lipid metabolism in Zucker fatty rats. *J Nutr* 2007; **137**: 1908-1915 [PMID: 17634263]

76 **Alvarez JA**, Ashraf A. Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis. *Int J Endocrinol* 2010; **2010**: 351385 [PMID: 20011094]

77 **Roth CL**, Elfers CT, Figlewicz DP, Melhorn SJ, Morton GJ, Hoofnagle A, Yeh MM, Nelson JE, Kowdley KV. Vitamin D deficiency in obese rats exacerbates nonalcoholic fatty liver disease and increases hepatic resistin and Toll-like receptor activation. *Hepatology* 2012; **55**: 1103-1111 [PMID: 21994008 DOI: 10.1002/hep.24737]

78 **Manco M**, Ciampalini P, Nobili V. Low levels of 25-hydroxyvitamin D(3) in children with biopsy-proven nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 2229; author reply 2230 [PMID: 20513013 DOI: 10.1002/hep.23724]

79 **Wu CC**, Chang JH, Chen CC, Su SB, Yang LK, Ma WY, Zheng CM, Diang LK, Lu KC. Calcitriol treatment attenuates inflammation and oxidative stress in hemodialysis patients with secondary hyperparathyroidism. *Tohoku J Exp Med* 2011; **223**: 153-159 [PMID: 21350317 DOI: 10.1620/tjem.223.153]

80 **Barchetta I**, Carotti S, Labbadia G, Gentilucci UV, Muda AO, Angelico F, Silecchia G, Leonetti F, Fraioli A, Picardi A, Morini S, Cavallo MG. Liver vitamin D receptor, CYP2R1, and CYP27A1 expression: relationship with liver histology and vitamin D3 levels in patients with nonalcoholic steatohepatitis or hepatitis C virus. *Hepatology* 2012; **56**: 2180-2187 [PMID: 22753133 DOI: 10.1002/hep.25930]

81 **Rhee EJ**, Kim MK, Park SE, Park CY, Baek KH, Lee WY, Kang MI, Park SW, Kim SW, Oh KW. High serum vitamin D levels reduce the risk for nonalcoholic fatty liver disease in healthy men independent of metabolic syndrome. *Endocr J* 2013; **60**: 743-752 [PMID: 23411507 DOI: 10.1507/endocrj.EJ12-0387]

82 **Targher G**, Bertolini L, Scala L, Cigolini M, Zenari L, Falezza G, Arcaro G. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis* 2007; **17**: 517-524 [PMID: 16928437 DOI: 10.1507/endocrj.EJ12-0387]

83 **Yang L**, Seki E. Toll-like receptors in liver fibrosis: cellular crosstalk and mechanisms. *Front Physiol* 2012; **3**: 138 [PMID: 22661952]

84 **Gratz SW**, Mykkanen H, El-Nezami HS. Probiotics and gut health: a special focus on liver diseases. *World J Gastroenterol* 2010; **16**: 403-410 [PMID: 20101763 DOI: 10.3748/wjg.v16.i4.403]

85 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID: 11961152 DOI: 10.1056/NEJMra011775]

86 **Compare D**, Coccoli P, Rocco A, Nardone OM, De Maria S, Cartenì M, Nardone G. Gut--liver axis: the impact of gut microbiota on non alcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis* 2012; **22**: 471-476 [PMID: 22546554]

87 **Miele L**, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, Mascianà R, Forgione A, Gabrieli ML, Perotti G, Vecchio FM, Rapaccini G, Gasbarrini G, Day CP, Grieco A. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* 2009; **49**: 1877-1887 [PMID: 19291785 DOI: 10.1002/hep.22848]

88 **Iacono A**, Raso GM, Canani RB, Calignano A, Meli R. Probiotics as an emerging therapeutic strategy to treat NAFLD: focus on molecular and biochemical mechanisms. *J Nutr Biochem* 2011; **22**: 699-711 [PMID: 21292470 DOI: 10.1016/j.jnutbio.2010.10.002]

89 **Li Z**, Yang S, Lin H, Huang J, Watkins PA, Moser AB, Desimone C, Song XY, Diehl AM. Probiotics and antibodies to TNF inhibit inflammatory activity and improve nonalcoholic fatty liver disease. *Hepatology* 2003; **37**: 343-350 [PMID: 12540784 DOI: 10.1053/jhep.2003.50048]

90 **Velayudham A**, Dolganiuc A, Ellis M, Petrasek J, Kodys K, Mandrekar P, Szabo G. VSL#3 probiotic treatment attenuates fibrosis without changes in steatohepatitis in a diet-induced nonalcoholic steatohepatitis model in mice. *Hepatology* 2009; **49**: 989-997 [PMID: 19115316 DOI: 10.1002/hep.22711]

91 **Ma X**, Hua J, Li Z. Probiotics improve high fat diet-induced hepatic steatosis and insulin resistance by increasing hepatic NKT cells. *J Hepatol* 2008; **49**: 821-830 [PMID: 18674841 DOI: 10.1016/j.jhep.2008.05.025]

92 **Shavakhi A**, Minakari M, Firouzian H, Assali R, Hekmatdoost A, Ferns G. Effect of a Probiotic and Metformin on Liver Aminotransferases in Non-alcoholic Steatohepatitis: A Double Blind Randomized Clinical Trial. *Int J Prev Med* 2013; **4**: 531-537 [PMID: 23930163]

93 **Eslamparast T**, Eghtesad S, Hekmatdoost A, Poustchi H. Probiotics and Nonalcoholic Fatty liver Disease. *Middle East J Dig Dis* 2013; **5**: 129-136 [PMID: 24829682]

94 **Eslamparast T**, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *Am J Clin Nutr* 2014; **99**: 535-542 [PMID: 24401715 DOI: 10.3945/ajcn.113.068890]

95 **Eslamparast T**, Zamani F, Hekmatdoost A, Sharafkhah M, Eghtesad S, Malekzadeh R, Poustchi H. Effects of synbiotic supplementation on insulin resistance in subjects with the metabolic syndrome: a randomised, double-blind, placebo-controlled pilot study. *Br J Nutr* 2014; **112**: 438-445 [PMID: 24848793 DOI: 10.1017/S0007114514000919]

96 **Ranasinghe P**, Jayawardana R, Galappaththy P, Constantine GR, de Vas Gunawardana N, Katulanda P. Efficacy and safety of 'true' cinnamon (Cinnamomum zeylanicum) as a pharmaceutical agent in diabetes: a systematic review and meta-analysis. *Diabet Med* 2012; **29**: 1480-1492 [PMID: 22671971 DOI: 10.1111/j.1464-5491.2012.03718.x]

97 **Askari F**, Rashidkhani B, Hekmatdoost A. Cinnamon may have therapeutic benefits on lipid profile, liver enzymes, insulin resistance, and high-sensitivity C-reactive protein in nonalcoholic fatty liver disease patients. *Nutr Res* 2014; **34**: 143-148 [PMID: 24461315 DOI: 10.1016/j.nutres.2013.11.005]

98 **Vera-Ramirez L**, Pérez-Lopez P, Varela-Lopez A, Ramirez-Tortosa M, Battino M, Quiles JL. Curcumin and liver disease. *Biofactors* 2013; **39**: 88-100 [PMID: 23303639 DOI: 10.1002/biof.1057]

99 **Girish C**, Pradhan SC. Hepatoprotective activities of picroliv, curcumin, and ellagic acid compared to silymarin on carbon-tetrachloride-induced liver toxicity in mice. *J Pharmacol Pharmacother* 2012; **3**: 149-155 [PMID: 22629090 DOI: 10.4103/0976-500X.95515]

100 **Shao W**, Yu Z, Chiang Y, Yang Y, Chai T, Foltz W, Lu H, Fantus IG, Jin T. Curcumin prevents high fat diet induced insulin resistance and obesity via attenuating lipogenesis in liver and inflammatory pathway in adipocytes. *PLoS One* 2012; **7**: e28784 [PMID: 22253696 DOI: 10.1371/journal.pone.0028784]

101 **Zhang J**, Xu L, Zhang L, Ying Z, Su W, Wang T. Curcumin attenuates D-galactosamine/lipopolysaccharide-induced liver injury and mitochondrial dysfunction in mice. *J Nutr* 2014; **144**: 1211-1218 [PMID: 24899159 DOI: 10.3945/jn.114.193573]

102 **Kuo JJ**, Chang HH, Tsai TH, Lee TY. Positive effect of curcumin on inflammation and mitochondrial dysfunction in obese mice with liver steatosis. *Int J Mol Med* 2012; **30**: 673-679 [PMID: 22751848 DOI: 10.3892/ijmm.2012.1049]

103 **Weidmann AE**. Dihydroquercetin: More than just an impurity? *Eur J Pharmacol* 2012; **684**: 19-26 [PMID: 22513183 DOI: 10.1016/j.ejphar.2012.03.035]

104 **Aguirre L**, Portillo MP, Hijona E, Bujanda L. Effects of resveratrol and other polyphenols in hepatic steatosis. *World J Gastroenterol* 2014; **20**: 7366-7380 [PMID: 24966607 DOI: 10.3748/wjg.v20.i23.7366]

105 **Zhang MH**, Liang ZQ, Qin Q, Li SL, Zhou DS, Tang L. [Effects of quercetin on serum levels of resistin and IL-18 and on insulin resistance in nonalcoholic fatty liver disease rats]. *Zhonghua Gan Zang Bing Za Zhi* 2013; **21**: 66-70 [PMID: 23663767]

106 **Lim CY**, Jun DW, Jang SS, Cho WK, Chae JD, Jun JH. Effects of carnitine on peripheral blood mitochondrial DNA copy number and liver function in non-alcoholic fatty liver disease. *Korean J Gastroenterol* 2010; **55**: 384-389 [PMID: 20571306 DOI: 201006256]

107 **Malaguarnera M**, Gargante MP, Russo C, Antic T, Vacante M, Malaguarnera M, Avitabile T, Li Volti G, Galvano F. L-carnitine supplementation to diet: a new tool in treatment of nonalcoholic steatohepatitis--a randomized and controlled clinical trial. *Am J Gastroenterol* 2010; **105**: 1338-1345 [PMID: 20068559 DOI: 10.1038/ajg.2009.719]

**P-Reviewer:** Kayadibi H,Tiniakos DG **S-Editor:** Ji FF **L-Editor: E-Editor:**