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REVIEW

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

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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.

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.

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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]. 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]. 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 (H^1-MRS) and Fibroscan are noninvasive modalities for diagnosis and staging, assessing a larger section of the liver in comparison to liver biopsy[3,4]. 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]. Developing effective therapies with minimal side-effects against NAFLD is critical for controlling the progression of this disease to end-stage liver disorders[6].

EPIDEMIOLOGY

NAFLD is the most common diagnosis in subjects with altered aminotransferases in the Western world[7], where one third of the population is affected[8]. In Asia, recent reports showed a similar prevalence of NAFLD[9,10]. About 20%-25% of adults with NASH have been reported to develop liver cirrhosis[11]. About 30% to 40% of patients who develop cirrhosis secondary to NAFLD, will die of liver-related problems[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]. 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]. 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]. NAFLD affects 40%-75% of patients with T2DM, 33%-76% of obese and 90% of morbidly obese people[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[12,17]. 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]. 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], such as oxidative stress, lipid peroxidation, increased inflammatory responses, hepatic fibrosis and apoptosis[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[21,22].

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)[11,23,24]. 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[25,26].

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]. 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 antioxidants 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]. Akcam *et al*[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]. 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]. 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]. 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]. 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], through the activation of AMPK[35,36], by induction of skeletal muscle SIRT1 and SIRT4 expression[37], by increasing the number of mitochondria, and specially, by increasing hepatic uncoupling protein 2 expression[38], decreasing hepatic LDL receptor and SR-BI mRNA and protein expressions[39], and the reduction of nuclear factor-kappaB (NF-kappaB) activity[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]. A different trial however, did find a significant improvement in NAFLD characteristics after 12 wk of supplementation with 500 mg Resveratrol[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].

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]. There is only one study evaluating the effects of ACN on NAFLD patients; Suda *et al*[45] have reported that supplementation with 400 mg 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]. 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]. 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].

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]. 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].

Coffee: Both epidemiological and animal studies have shown that drinking coffee on a regular basis can decrease the risk of T2DM development[49-51]. 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]. Among NASH patients, coffee consumption has been shown to be significantly associated with a reduced risk of fibrosis[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[54,55].

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]. 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[57,58].

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]. 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]. 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]. 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]. They are also thought to exert anti-inflammatory effects[65]. N-3 fatty acids affect lipid metabolism by mediating genomic pathways and regulating the transcription of genes involved in lipid metabolism[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)[67,68]. Several studies support the protective effects of n-3 PUFAs in NAFLD. Among these, Capanni *et al*[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]. 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]. 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]. 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], and in the reduction of inflammation[73], as well as to their inhibitory effects on nuclear factor-κB (NF-κB)[74]. In a study, MUFA decreased the expression of hepatic lipogenesis and gluconeogenesis genes and SREBP in fatty rats[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]. 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]. In humans, vitamin D deficiency has been correlated with a more severe NAFLD activity score and hepatic fibrosis[78], perhaps owing to the greater oxidative stress resulting from vitamin D deficiency[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]. A recent study found a significant association between NAFLD and low serum vitamin D levels[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]. 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[83,84]. The gut-liver axis is an important pathway in NAFLD development, which is associated with small intestinal bacterial overgrowth and increased intestinal permeability[85,86]. 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[87,88].

Probiotics are live microorganisms that are beneficial to human health when ingested[88]. The therapeutic effects of probiotics have been demonstrated in several animal models of NAFLD[86,89-91]; however clinical trials are scarce[92-95]. 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].

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].

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]. 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[98,99]. Curcumin can reduce the expression of lipogenic genes in the liver and inflammatory responses of adipose tissue[100], while enhancing the antioxidant defense system, attenuating mitochondrial dysfunction and inhibiting apoptosis[101,102]. 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]. Studies have demonstrated that quercetin can modestly reduce weight and regulate the expression of genes related to *in vitro* adipogenesis[103,104]. Quercetin reduces inflammatory cytokine levels and improves lipid peroxidation and insulin resistance in animal models of NAFLD, and its beneficial effects are dose dependent[103,105]. 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]. 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]; 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.

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