



# Medical nutrition therapeutic approach of non-alcoholic fatty liver: diet, nutraceuticals, phytotherapy and probiotics

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## Abstract

Although the genetic and pharmacological research of the non-alcoholic fatty liver disease (NAFLD), the commonest liver disease in the world, affecting more than a quarter of the population, shows a promising future, the non-pharmacological therapy continues to be an important approach of this concerning public health issue. The present study focused on the therapeutical potential of the diet and mainly the phytotherapy, nutraceuticals, and probiotics use, employing the literature review methodology by a selection of recent (last 5-10 years) national and international articles from the PubMed and Google Scholar databases. The conclusion was that the non-pharmacological medical nutrition approach could be considered as a first-line therapeutical option for NAFLD due to its low cost, few adverse effects, and a mainly positive impact on an individual's health and life quality.

**Keywords:** Liver steatosis. Therapy. NAFLD. Therapy. Phytotherapy. Probiotics.

## Introduction

Hepatic steatosis (HS) represents the accumulation of lipids in liver cells and can be classified into 2 main forms, one found in association with chronic alcohol intake and the other without a history of alcohol use [1,2]. Alcoholic fatty liver or Alcohol-related liver disease (ARLD) has a prevalence of 10-20% in the adult population worldwide and is related to the use of more than 24 g of alcohol/day in women and more than 36 g of alcohol per day in men and develops due to malnutrition, the toxicity of ethanol through the formation of formaldehyde via the alcohol

dehydrogenase and cytochrome P540 2E1 pathways and the increased synthesis of fatty acids through the reduced form of the nicotinamide adenine dinucleotide (NADH) [3]. In the case of steatosis with no history of alcohol use (less than 24/36 g of alcohol per day), we have Non-alcoholic fatty liver disease or Non-alcoholic fatty liver disease (NAFLD) with an even higher prevalence of more than a quarter of the world's population [4].

According to etiological factors, the vast majority of cases are related to obesity, insulin resistance, and metabolic syndrome, but we also have hepatic steatosis related to nutritional deficiencies or toxicity by various exogenous substances. Among the toxic causes of NAFLD is exposure to polycyclic aromatic hydrocarbons (due to air pollution or smoking), metals such as cadmium and we also have a small percentage of iatrogenic NAFLD cases, induced by drugs such as valproic acid, tetracycline, aspirin, ibuprofen, indomethacin, tamoxifen, amiodarone, propranolol, zidovudine or vitamin A [2,3].

In the etiopathogenesis of NAFLD, the current theory of "multiple hit" considers several injuries acting together in individuals with genetic predisposition, considering that nutritional, genetic, and environmental factors can determine the development of insulin resistance and obesity with the proliferation of adipocytes and increased secretion of adipokines and inflammatory cytokines by adipose tissue. Adding changes in the intestinal microbiome with the production of fatty acids in the intestine, the increase in intestinal permeability and absorption of fatty acids, and the activation of inflammatory pathways with the release of IL-6 and TNF- $\alpha$ , we have an increase in hepatic neolipogenesis and hepatic lipotoxicity with mitochondrial dysfunction and increased oxidative stress by the production of reactive oxygen species (ROS) free radicals [5].

The prevalence of NAFLD in the adult population varies by region and population, 20% in Brazil, between 22 and 28% of the European adult population reaching 30% in Germany, 40% in the US, and 60% in China, generating high risks of and, consequently, considerable costs to the health system. The high numbers are related to the high prevalence of diabetes, insulin resistance, and obesity in these geographic regions, in the diabetic population the prevalence of NAFLD increasing to up to 70% to reach 80% in an obese population. In addition to its high prevalence worldwide and the specific risk of its evolution, non-alcoholic steatohepatitis (NASH) of progressing to liver cirrhosis and hepatocellular carcinoma, its complex interrelationship with diabetes and cardiovascular disease determines health risks in general and an association with increased mortality from cardiovascular events and mortality in general [6]. These risks to the health of the population make NAFLD a public health problem worldwide and require multidisciplinary treatment of the disease, including nutritional monitoring and pharmacological and non-pharmacological treatment.

Due to the scarce availability, the current high cost of efficient pharmacological therapeutic solutions, and the importance of non-pharmacological treatment, the present work aimed to carry out a literature review on the non-pharmacological nutritional approach of NAFLD to summarize the treatment alternatives through the use of vitamins, food supplements, plant derivatives, and probiotics.

## Methods

### Study Design

The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews and meta-analysis-[HTTP://www.prisma-statement.org/](http://www.prisma-statement.org/)) were followed [7].

### Data sources and research strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "liver steatosis, non-alcoholic fatty liver disease, NAFLD, therapy, phytotherapy, probiotics". The research was carried out in the PubMed and Scielo, com referências de 2011 a 2021. Also, a combination of the keywords with the booleans "OR", "AND" and "NOT" were used to target the scientific articles of interest.

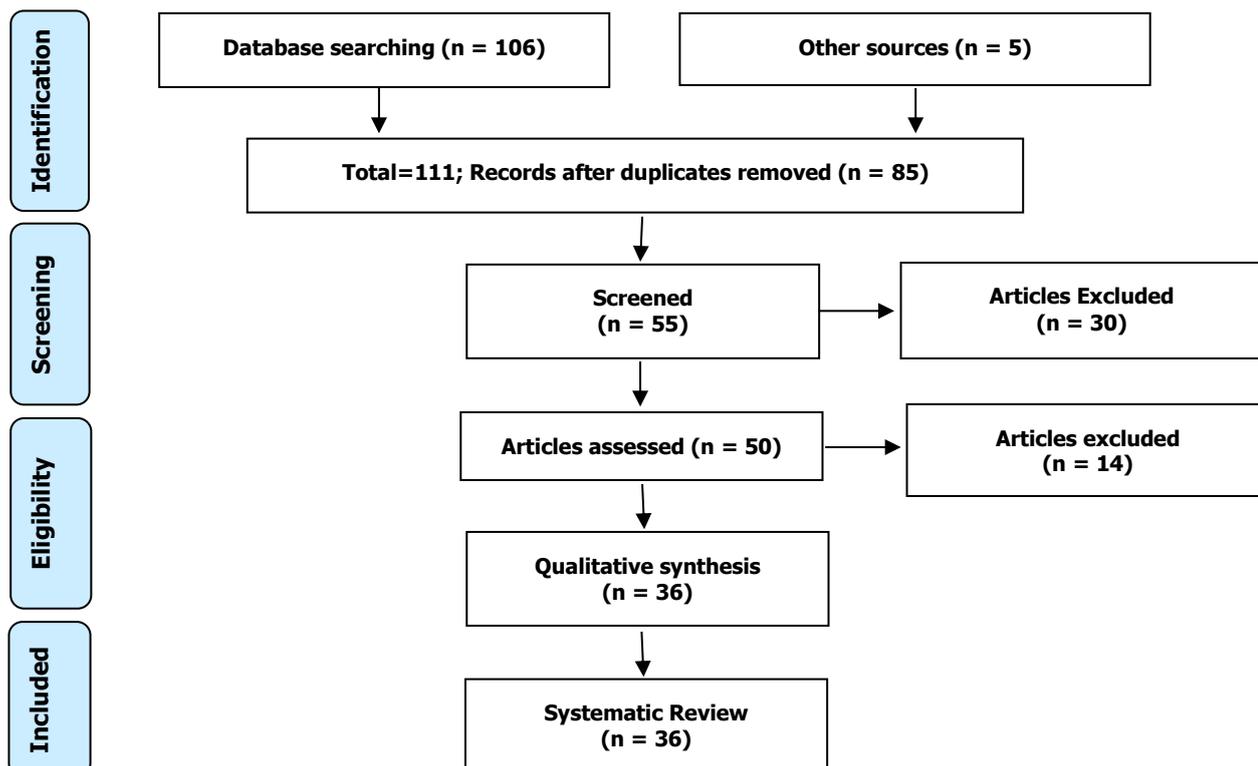
### Study Quality and Bias Risk

The quality of the studies was based on the GRADE instrument [8] and the risk of bias was analyzed according to the Cochrane instrument [9].

## Results and Discussion

A total of 111 studies were found that were submitted to the eligibility analysis, and, after that, 36 studies of high to medium quality and with risks of bias were selected that do not compromise the scientific basis of the studies (Figure 1).

Figure 1. Study eligibility.



## Results and Development

The treatment of NAFLD depends on the disease's etiopathogenesis, according to the "multiple hit" etiopathogenic theory, which considers several injuries acting together in individuals with genetic predisposition [5]. The nutrological approach of NAFLD starts with the identification of etiological factors (according to the aforementioned theory), the diagnosis of associated predisposing pathologies such as obesity, insulin resistance, and type 2 diabetes mellitus, whose most common complication is considered, continuing with the treatment of these pathologies.

Pharmacological treatment includes the treatment of these comorbidities, drugs such as glitazones or GLP1 analogs (exenatide, liraglutide, or semaglutide) showing promising therapeutic results not only in the therapy of diabetes mellitus and obesity but also in hepatic steatosis. In addition to bariatric (metabolic) surgery, reserved for patients with morbid obesity and the practice of specific physical activity, non-pharmacological treatment consists mainly of lifestyle changes, diet therapy, herbal medicine, and the use of probiotics [1].

Even though there is currently no treatment for genetic predisposition, it is important to have a diagnosis of genetic and epigenetic factors to be able to predict the risks and severity of the evolution and adjust the aggressiveness of the therapy for better efficiency. Research has shown that patatin-like phospholipase 3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2) polymorphism influence the development of NAFLD and the risk of progression to NASH. At the same time, some alleles such as 148 in PNPLA3 and 167Lys in TM6SF2 with a greater genetic predisposition to NAFLD are associated with the protection or increased risk for cardiovascular diseases suggesting the need for an individualized, specific approach in these cases [4,6].

Studies of epigenetic factors in animal models have an impact on the NAFLD approach, suggesting possible therapies, such as betaine administration, associated with increased output of triglycerides from the liver, folate replacement, whose deficiency produces an accumulation of triglycerides in the liver or methionine and choline whose deficiencies can determine NASH [3].

The basis of the nutritional approach is the purpose of correcting the dietary factors that determine the development of NAFLD (and NASH) and the comorbidities of insulin resistance [10], type 2 diabetes mellitus, and obesity. As one of the main etiological factors is the increased caloric intake [11], which rapidly determines the increase in hepatic steatosis, its adequacy to the energy requirement is the first measure to be taken.

In terms of quality and macronutrients, it is important to control carbohydrate intake in general and fructose in particular, especially the industrialized form, a known lipogenic and pro-inflammatory factor that increases oxidative stress and TNF- $\alpha$  [10].

The increase in fat intake in general and especially saturated fat also has consequences on the appearance and evolution of hepatic steatosis, with level A evidence on the therapeutic efficiency of its reduction in the menu. A higher incidence of NAFLD is associated with a higher intake of protein, mainly from red meat [12,14], and with a reduced intake of fiber. This increased risk associated with the modern western dietary pattern, with increased caloric intake, simple carbohydrates, and industrialized fructose, fat, mainly saturated and red meat associated with a low fiber intake explains the high prevalence of this liver disease and also indicates how the best food options for the prevention and treatment of hepatic steatosis are the DASH and Mediterranean diets, with the latter being more effective [12,15].

A particular aspect of the Mediterranean diet is the richness of omega-3 polyunsaturated fatty acids (PUFA) such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids of marine origin that can decrease plasma triacylglycerides (TAG) and modulate lipid metabolism, increasing beta fatty acid oxidation and decreasing neolipogenesis by decreasing hepatic steatosis in NAFLD. The same therapeutic effect was observed in the case of supplementation with 1 g/day of omega-3 PUFAs of marine origin (fish oil) or vegetable (linseed oil) [16].

Several studies recommend the following composition of macronutrients: carbohydrates 45-65% of the daily caloric requirement (with a preference for whole grains and low glycemic index foods, resistant starch, fructooligosaccharides (FOS), avoiding simple and refined sugars and foods rich in fructose), low lipid intake, 30-35% of the daily caloric requirement (avoiding trans and saturated fats and giving preference to olive oils, seeds, nuts, fish) and protein 15-20% of the daily caloric requirement, with increased vegetable, milk, chicken and fish proteins and a reduction in red meat, especially processed meat, as shown in Table 1 [12,15,17].

In addition to macronutrients, the presence of plant fibers in the diet, especially prebiotic fibers, which are substrates for probiotics, has a beneficial effect by reducing caloric intake and intestinal microbiota alteration. Among the soluble fibers are pectins, FOS, inulin, gums, beta-glucan, and psyllium, found in fruits, vegetables, and grains. Plantago ovata, a plant rich in psyllium, a soluble fiber-rich in mucin that reduces the absorption of lipids, increasing gastric fullness, and intestinal transit, is used in

**Table 1.** Recommendation for intake of macronutrients and fiber in NAFLD.

Food Composition	% of energy requirement	Recommended foods	Foods to avoid
<b>Carbohydrates</b>	45-65%	- Low Glycemic Index Whole Grains	- simple, refined sugars - rich in fructose
<b>Lipids</b>	<30-35%	- olive oil, nuts, seeds, fish	- trans fat - saturated fat
<b>Proteins</b>	15-20%	- vegetable protein, milk, chicken, fish	- red meat - processed meat
<b>Fibers</b>	****	- fruits, vegetables - whole grains and flours	- refined foods

doses of 1-1.5 g/day associated with increased intake of water. *Chlorella pyrenoidosa*, a unicellular alga rich not only insoluble fiber but also in proteins, essential fatty acids, minerals, and antioxidants has not only a detoxifying action but also an anti-obesogenic action by reducing the absorption of intestinal fat and carbohydrates and by increasing the sensation of gastric fullness and intestinal transit due to fiber content [18].

It is used in a dose of 1-2 g/day, before a meal, also associated with an increase in water intake. Among micronutrients, copper is the main biometal involved in redox reactions and although the best-known case of liver injury is due to its accumulation in the liver in hereditary hemochromatosis, some animal studies have shown that its restriction also induces changes in lipid metabolism, insulin resistance, and hepatic steatosis [18], probably due to increased oxidative stress. The copper-binding ability of some antioxidants such as curcumin, EGCG, quercetin, and resveratrol could be related to their hepatoprotective actions.

Another metal, iron, has a still-controversial role, some studies showing that iron deficiency is prevalent in patients with NAFLD and obesity, especially in non-Caucasian women [19] or a decrease in physical activity capacity when NAFLD is associated with iron deficiency [20], even though it is not the cause of NAFLD or obesity. At the same time, an increased tissue iron level is a risk factor for several chronic diseases such as diabetes and NAFLD and some studies suggest that a low tissue iron level is a protective factor for progression to NASH [21]. Although an increase in ferritin appears in NAFLD, it is more often found related to inflammation and only in some cases, in men, related to increased tissue iron [22], so there is no specific recommended approach regarding iron.

Although chromium may be involved in the

development of insulin resistance and its supplementation appears to have beneficial effects on glycemic control in type 2 diabetes and metabolic syndrome (but without impact on lipid profile, body composition, and obesity), more studies are needed to clarify their mechanisms of action, their effectiveness and safety related to prolonged use [23]. Coffee intake (more than 3 /day) is considered a protective factor for the evolution of NASH, due to the antioxidant, anti-inflammatory, and antifibrotic effects [21,24] of caffeine and the contained antioxidants. Moderate alcohol consumption (0.5-1.5 drinks/day) shows a significant protective effect with a mortality reduction of up to 41% in patients with NAFLD [25], possibly through activation of the sirtuin1/adiponectin pathway in tissue adipose.

The consumption of green tea, produced with *Camellia sinensis* leaves, also showed a protective effect, probably due to epigallocatechin 3-gallate (EGCG) which affects lipid and glucose metabolism, reducing lipid peroxidation, with anti-inflammatory and anti-fibrosis [26]. The presence of caffeine potentiates the effect of EGCG, stimulating metabolism by inhibiting phosphodiesterase, increasing cAMP, and reducing lipid levels in the blood. In addition to being used as an infusion, it can be administered as a dry extract at a dose of 600-800 mg/day

Importantly, fruits, vegetables, and more complex plant extracts have superior effects to supplements containing isolated phytochemicals due to the synergistic effect of the various components while most quality studies are performed with isolated phytochemicals. Astaxanthin, a carotenoid present in salmon and shrimp with a strong antioxidant effect, has shown anti-liver fibrosis effects in animal studies, but the mechanism of action still needs to be studied, as well as its effects in humans. Curcumin, the polyphenol from

Turmeric Longa, in addition to its general anti-inflammatory, antioxidant, antiviral, and anti-cancer effects has an anti-liver fibrosis effect by inhibiting the expression of TGF $\beta$ 1. Blueberry can also prevent liver fibrosis due to its antioxidant capacity by increasing SOD activity [27].

Resveratrol, the flavonoid found in grapes and berries, also has an anti-fibrosis effect through its antioxidant and anti-inflammatory properties. Some animal studies have shown that the association of resveratrol with moderate calorie restriction (30%) can also activate sirtuin 1 (SIRT1) and induce autophagy with improvement in hepatic steatosis and body composition [28].

Silymarin, the extract of *Silybum marianum*, contains the flavonoid taxifolin and flavonolignans and has proven hepatoprotective, anti-inflammatory, and antioxidant properties, also increasing hepatocyte regeneration [29]. Among the vitamins, vitamin E is considered an on-label therapy for hepatic steatosis, at a dose of 800 IU/day. Some studies show that vitamin C intake (dose of 90-180 mg/day) also has a moderate inverse association with NAFLD, but only in a non-obese male population over 40 years of age [30].

Although some studies suggest that the intake of vitamins D and A also has a protective effect [27], probably through the antioxidant effect, the serum level of 25(OH)vitamin D showing an inverse association with NAFLD [31] further studies are needed, mainly on vitamin D, the vitamin D receptor (VDR) and its influence on the intestinal microbiome. A relatively new concept that has gained popularity, the so-called "gut-liver axis" reveals the impact of the intestinal microbiome on the liver, which receives more than 50% of the blood from the splanchnic territory and represents the first line of defense against bacteria and toxic products. In these conditions, an increase in intestinal permeability due to dysbiosis results in an exposure of the liver to an increase in lipopolysaccharides (LPS), one of the most toxic bacterial products, with the activation of an inflammatory cascade that determines insulin resistance, obesity, and NAFLD or NASH [32].

Some studies have shown that individuals with insulin resistance have higher serum levels of branched-chain amino acids (BCAA) which have been linked to an increased prevalence of *Prevotella copri* and *Bacteroides vulgatus* in the intestinal microbiome [32]. Due to the strong association of insulin resistance with NAFLD, the severity of hepatic steatosis is related to the degree of intestinal dysbiosis and the modulation of the intestinal microbiota with antibiotics and probiotics determined an improvement in insulin resistance and a reduction in

visceral fat [33]. The use of fermented milk and probiotics (*Lactobacillus* and *Bifidobacterium*) led to an improvement in the lipid profile, with a reduction in total cholesterol, LDL, and triglycerides, also being responsible for the increase in HDL and the reduction of ALT and AST levels in patients NAFLD carriers. One of the lesser-known etiologies of NAFLD is the endogenous production of alcohol due to the existence of the alcohol-producing strain of *Klebsiella pneumonia* (HiAlcKpn) in the intestinal microbiota. One study showed that intestinal colonization with HiAlcKpn is associated with up to 60% of NAFLD cases in a Chinese population and that fecal transplantation of this strain in rats induces the development of NAFLD [33]. These findings also propose the level of serum alcohol after ingestion of glucose as a biomarker that reflects both the level of HiAlcKpn in the gut microbiota as well as the evolution of NAFLD. The use of prebiotics is part of the intestinal microbiota modulation therapy including fruits, grains, or specific products such as FOS, inulin, or psyllium.

These data show the importance of the gut microbiome and recommend its modulation as a potential therapy for insulin resistance and NAFLD but further studies with cohorts and longer intervention periods are needed to determine quantitative and qualitative parameters of the gut microbiota associated with NAFLD, essential data for a more specific future approach [34,35].

Finally, a study evaluated the effectiveness of probiotic and prebiotic supplementation on metabolic parameters, liver enzymes, and inflammation in patients with NAFLD. In this study, NAFLD patients were assigned to receive probiotic capsule + prebiotic placebo (probiotic group), oligofructose + probiotic placebo (prebiotic group), or probiotic placebo + prebiotic placebo (control group) for 12 weeks. Anthropometric measurements decreased in all three groups, but there was no significant difference between groups. Probiotic supplementation was able to decrease triglycerides, alanine aminotransferase, aspartate aminotransferase,  $\gamma$ -glutamyltransferase, and alkaline phosphatase compared to the control group. High-sensitivity C-reactive protein significantly decreased in all groups [36].

## Conclusion

Given the high prevalence of NAFLD and complications, both hepatic and cardiovascular, with increased overall morbidity and mortality, this pathology has become a problem for the health system worldwide, with an important financial and quality of life impact. Therapeutic options such as bariatric surgery (metabolic)

or pharmacological therapy (with pioglitazone, GLP1 analogs such as liraglutide, exenatide, or semaglutide) show promising results but have a high cost and several adverse effects, sometimes negatively impacting the patient's quality of life. Under these conditions, non-pharmacological therapy continues to be the basis for the treatment and prevention of hepatic steatosis not related to alcohol use, the nutritional approach with diet therapy, nutraceuticals, plant derivatives, and probiotics is considered first-line treatment. New studies are needed, both translational and mainly prospective studies, with larger cohorts and intervention times, and also employing better techniques to determine the degree of hepatic steatosis to assess the efficacy of therapeutic alternatives, standardize them and create treatment algorithms.

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No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

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