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Nutraceutical approaches to non-alcoholic fatty liver disease (NAFLD): A position paper from the International Lipid Expert Panel (ILEP)

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ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a common condition affecting around 10–25% of the general adult population, 15% of children, and even > 50% of individuals who have type 2 diabetes mellitus. It is a major cause of liver-related morbidity, and cardiovascular (CV) mortality is a common cause of death. In addition to being the initial step of irreversible alterations of the liver parenchyma causing cirrhosis, about 1/6 of those who develop NASH are at risk also developing CV disease (CVD). More recently the acronym MAFLD (Metabolic Associated Fatty Liver Disease) has been preferred by many European and US specialists, providing a clearer message on the metabolic etiology of the disease.

The suggestions for the management of NAFLD are like those recommended by guidelines for CVD prevention. In this context, the general approach is to prescribe physical activity and dietary changes the effect weight loss. Lifestyle change in the NAFLD patient has been supplemented in some by the use of nutraceuticals, but the evidence based for these remains uncertain. The aim of this Position Paper was to summarize the clinical evidence relating to the effect of nutraceuticals on NAFLD-related parameters. Our reading of the data is that whilst many nutraceuticals have been studied in relation to NAFLD, none have sufficient evidence to recommend their routine use; robust trials are required to appropriately address efficacy and safety.

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1. Introduction

The liver is involved in several functions, including glucose and lipid metabolism. The roles in carbohydrate metabolism include gluconeogenesis, glycogenolysis, and glycogen synthesis. The liver is closely involved in lipid and lipoprotein metabolism through apolipoprotein synthesis, cholesterol and triglycerides synthesis, assembly of lipoproteins and the elimination cholesterol via the biliary route[1]. The bile produced by the liver is also essential for emulsifying lipids (including fat-soluble vitamins) in the intestine, thus allowing the absorption of nutrients [1].

Intracellular fat accumulation in the liver is called liver steatosis and can occur as a result of excessive alcohol intake (Alcoholic Fatty Liver Disease, AFLD) or other metabolic factors (Non-Alcoholic Fatty Liver Disease, NAFLD). The internationally accepted threshold level chosen by the Scientific Community to distinguish AFLD from NAFLD is the amount of 2 drinks (the equivalent of 20 g ethanol) per day[2]. NAFLD is a very common condition affecting 25-30% of the general adult population, 15% of children, and >50% of individuals who are overweight, obese or have type 2 diabetes mellitus (T2DM)[3]. NAFLD is considered reversible [3]. It is a major cause of liver-related and cardiovascular (CV) morbidity and mortality, especially its clinically aggressive variant, i.e., non-alcoholic steatohepatitis (NASH)[4,5].

NASH is characterized by inflammation and progressive tissue degeneration. NASH affects about 5% of the general adult population, and 20% of obese people[6]. The gold standard diagnosis for NAFLD and NASH is liver biopsy. However, the diagnosis of NAFLD is usually made by ultrasound ("bright liver"), after excluding other causes of chronic liver disease and alcohol intake of <20 g/day, and by using validated scores, such as the Fatty Liver Index (FLI), fibrosis score or others[7]. More recently, predictive models with the use of machine learning and omics are being developed as a noninvasive alternative to liver biopsy[8,9].

The main non-genetic risk factors for NAFLD are overweight/obesity, insulin resistance/T2DM, hypertriglyceridemia and dietary-behavioral triggers (e.g., the intake of beverages sweetened with fructose). In several observational studies[10], consumption of sugared soft drinks (mainly with fructose) has been shown to increase the risk of developing NAFLD by around 55%[11]. Emerging risk factors include tobacco smoking, obstructive sleep apnoea syndrome (OSAS), chronic obstructive pulmonary disease (COPD), insomnia and excessive daytime sleepiness unrelated to nocturnal sleep apnoea[12,13]. Furthermore, a strong association between hypothyroidism and NAFLD has recently been confirmed by a meta-analysis of 13 prospective studies that showed how hypothyroidism could increase the risk of NAFLD by >50%. The risk increases up to 70% if subclinical hypothyroidism is excluded[14]. However, the first risk factor is often related to poor lifestyle habits, including the high consumption of sweetened beverages and physical inactivity.

NAFLD is the initial step in the development of irreversible alterations of the liver parenchyma leading to cirrhosis (about 1/3 of the cases of NAFLD develop NASH, and 15% of these can progress to cirrhosis), while on the other hand, NAFLD can be *per se* a risk factor for the development of CV disease (CVD)[15] and T2DM[16]. Preliminary data suggest that NAFLD may also be associated with a greater incidence of hepatic and extra-hepatic oncogenesis[17,18]. Furthermore, a recent meta-analysis of 9 observational studies [19] providing data from 96, 595 adults (34.1% had NAFLD), with 4653 cases of moderate-to-severe renal failure, and a median observation period of 5.2 years, showed that patients with NAFLD had a 37% increased risk of developing chronic renal failure. The risk appeared to be related to the degree of lipid infiltration of the liver. Similarly, another meta-analysis involving 33 studies (63,902 participants) found the association between NAFLD and a higher risk of chronic kidney disease (CKD); and similarly, NASH and advanced fibrosis with more advanced CKD[19]. Considering that both renal failure and NAFLD are risk factors for CVD, it follows that this epidemiological association is of particular clinical relevance [20].

Another meta-analysis of six studies that included 25,837 patients (of whom 5953 had NAFLD) showed that patients with NAFLD had a relative risk of total CV events of 1.77 (95% CI 1.26-2.48, ^{p}<0.001)[21]. Specifically, the relative risk (RR) increased to 2.26 (95% CI: 1.04-4.92, ^{p}<0.001) for coronary artery disease and to 2.09 (95% CI: 1.46-2.98, ^{p}<0.001) for ischemic stroke. Furthermore, the presence of NAFLD significantly raised the RR of CV mortality to 1.46 (95% CI 1.31-1.64, ^{p}<0.001) [22].

Pending specific drug options, currently in phase 3 clinical trials, the main treatment of NAFLD involves lifestyle interventions aimed at weight loss and increased physical activity to reduce the extent of insulin resistance[22]. Since the risk factors for NAFLD are similar to those for CVD, the suggestions for the management of NAFLD are similar to those recommended by guidelines for CVD prevention[23]. Therefore, the general approach is to prescribe relatively low-calorie diets (with a caloric intake proportional to energy consumption), with predominantly low glycemic index carbohydrates, and to minimize the consumption of fructose, alcohol, as well as saturated and trans-unsaturated fats[24]. In particular, the adherence to a Mediterranean Diet is a significant predictor of decrease in liver fat content in patients with NAFLD[25]. The consumption of coffee is not recommended, but if coffee is already consumed by the patient, there is no recommendation for stopping its intake. Of note, a substantial body of evidence, summarized in a meta-analysis, suggests a lower risk of fibrosis in coffee drinkers with NAFLD[26]. Another meta-analysis reported that coffee consumption of >3 cups/day (compared with <2 cups) significantly reduced the occurrence of NAFLD, thus suggesting a potential dose-dependent association between coffee intake and NAFLD risk[27].

Physical activity should be encouraged and implemented, considering the intensity of training and any comorbidities present. In fact, a recent meta-analysis of 6 cohort studies involving 142,781 participants with 32,657 incident cases of NAFLD, as well as 4 case-control studies involving 382 affected patients and 302 controls, showed that the difference in the risk of developing NAFLD among sedentary and physically active individuals was 21% in observational studies and 57% in case-control studies[28]. Furthermore, regardless of the diet, the greater the frequency and intensity of physical activity, the greater the reduction of transaminase levels and the degree of hepatosteatosis, especially in overweight subjects[29].

Increasing evidence suggests that specific food supplements or nutraceuticals with confirmed hepatoprotective effects can be used to accelerate the improvement of liver enzymes and steatosis, or at least to slow down its progression (Fig. 1)[30]. This rationale becomes stronger when using nutraceuticals, which simultaneously reduce CV risk[31,32]. Therefore, this International Lipid Expert Panel (ILEP) Position Paper, aim to summarize the clinical evidence relating to the effect of nutraceuticals on NAFLD-associated parameters.

2. Organization of the position paper

While working on this Position Paper we strictly followed the ILEP scientific policy on the preparation of the recommendations. Briefly: (1) the idea on this paper was suggested by Prof. Manfredi Rizzo (MR), Dr. Alessandro Colletti (AC), Prof Arrigo F.G. Cicero (AFGC) and Prof. Maciej Banach (MB), which was formally sent to the Steering Committee of the ILEP (see: www.ilep.eu for details) for approval. Next, (2) official e-mail to all ILEP Members were sent, inviting them to be a part of the Writing Committee (WC) of this paper, in which we also presented the concrete tasks to be done and the detailed schedule on how to work with the paper. After establishment of the WC, (3) MR, AC, AFGC and MB started to work on the main content and scientific assumption of the paper, which were next presented to the members of the WC (due to pandemic time both using online platforms and via e-mails). Next, (4) together with selected members of the WC, we worked on the draft version of the recommendations, which were next extensively discussed

with all the WC members, putting specially emphasis on the management figures and tables with recommendations. In case of disagreement, each recommendation was voted. In the next step (5), the final draft of recommendations was sent to all ILEP members for the internal review process and approval. Each comment and suggestion from the ILEP members were responded and discussed.

A systematic search strategy was developed to identify randomized clinical trials (RCTs) and their meta-analyses in PubMed (from January 1970 to September 2021). The terms 'nutraceuticals', 'dietary supplements', 'herbal drug' and 'NAFLD', 'NASH' were incorporated into an electronic search strategy. The experts of the Writing Committee carefully discussed the available data on the safety and efficacy of the investigated nutraceuticals in NAFLD and then anonymously voted on the selection of those with the largest data available to be finally included in the recommendations. The experts also discussed and agreed on each recommendation level presented in the text of the Position Paper. The recommendations were approved by all ILEP Members.

For each selected nutraceutical, a short description of the mechanism of action has been reported, followed by the clinically observed effects and the most relevant tolerability notes. The strength of recommendation of the nutraceuticals' effect on liver steatosis and/or liver inflammation have been according to new scale suggested by the Panel, as outlined in Table 1· The experts of the writing and reviewing panels completed *Declaration of Interest* forms where any actual and/or potential conflicts of interest were presented.

Table 1
The strength of recommendation based on the quality of evidence available for each nutraceutical.

Symbol	Quality of Evidence	Explanation
++++	High	"Further research is very unlikely to change confidence in the estimate of effect."
+++O	Moderate	"Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate."
++OO	Low	"Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate."
+OOO	Very low	"Any estimate of effect is very uncertain."

3. Clinically evaluated nutraceuticals

3.1. Omega-3 fatty acids

Omega-3 (ω-3) fatty acids are polyunsaturated fatty acids (PUFAs) which, at least at alpha-linolenic acid (C18:3) are essential fatty acids since humans lack enzymes to introduce double bonds beyond the C-9 position of the carboxyl end (carbon beyond C-9 in the fatty acid chain) [33]. The PUFAs family includes several fatty acids such as α-linolenic acid (α-ALA), stearidonic acid (SDA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). Ω-3 are naturally present in animals (fish, krill, egg, and squid) and plants (algae, flaxseed, walnut, edible seeds, and clary sage)[34]. In recent years, the European Food Safety Authority (EFSA), the American Heart Association (AHA) and the Food Standards of Australia and New Zealand (FSANZ) have recognized ω-3 fatty acids as preventive nutraceuticals for CVD[35]. In this regard, the intake of at least 2 g/day of DHA and EPA has been recognized with a specific claim by the EFSA as having the ability to maintain normal circulating TG levels[36]. In humans, ω-3 fatty acids are involved in several biological activities, making them fundamental for the maintenance of the health status of different organs, including the liver. Although a balanced diet can theoretically provide an adequate amount of ω-3 fatty acids, the qualitative and biodiversity impoverishment of dietary components, methods of processing and cooking, and raised functional demands of the organism makes supplementation with ω-3 fatty acids increasingly necessary[37].

3.1.1. Mechanism of action

EPA and DHA are well known for their TG-lowering capacity which occurs via several mechanisms: reduced synthesis of hepatic very low-density lipoprotein (VLDL) and of TG-synthesizing enzymes (diacylglycerol acyltransferase or phosphatidic acid phosphohydrolase), reduced availability of substrates for the synthesis of new TG, reduced endogenous fatty acid synthesis, as well as increased β-oxidation of fatty

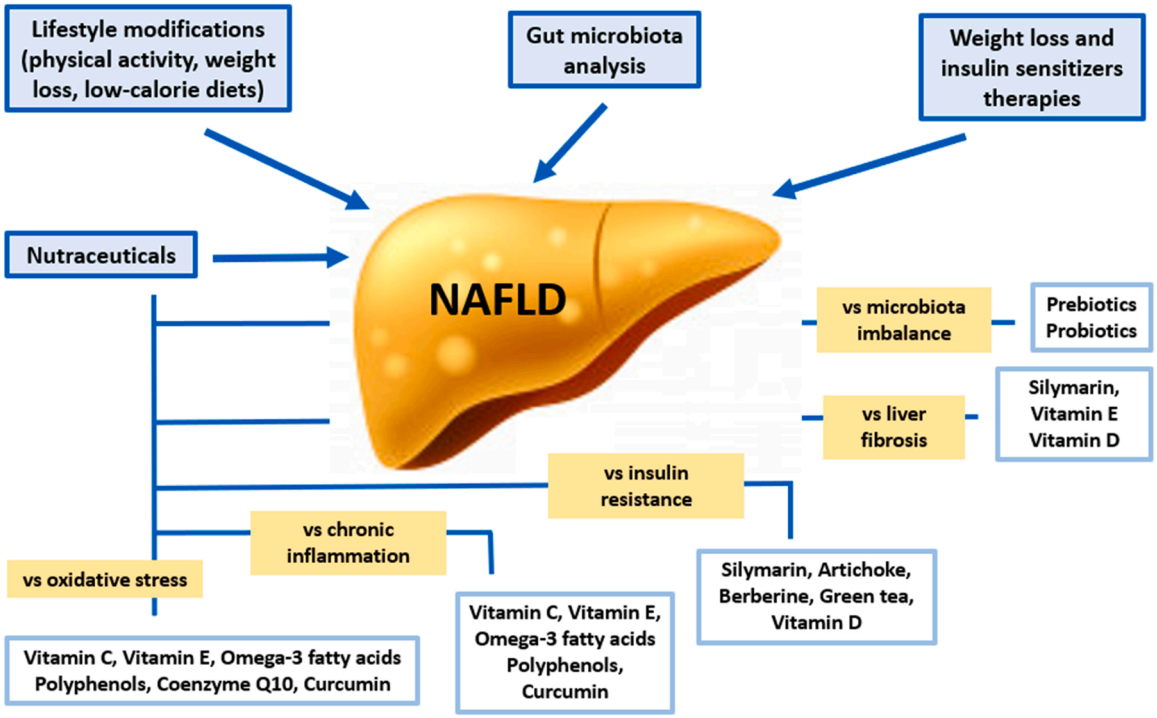

Fig. 1. Complementary approaches to NAFLD and main target of nutraceuticals.

acids and synthesis of phospholipids [38]. In addition, other studies proposed that ω-3 fatty acids could ameliorate insulin resistance by modulating mitochondrial function or mediating anti-inflammatory effects [39,40]. Moreover, EPA and DHA improve the phospholipid fatty acid composition of cell membranes, reduce the activity of NF-κB and modulate the activation of the anti-inflammatory transcription factor NR1C3, linked to an amelioration of liver inflammation [41]. In this context, both EPA and DHA have been demonstrated to down-regulate cytokines IL-6, TNF-α, MCP-1, ICAM-1, and to inhibit the NO formation-related gene pathway in NAFLD murine models [42]. Kim et al. reported that PUFAs may also increase the levels of lipolytic proteins, such as AMPK, and phosphorylation activity by acetyl-CoA carboxylase, while decreasing the levels of lipogenic proteins in the liver of high-fat diet-fed mice [43].

3.1.2. Efficacy

A meta-analysis conducted by Eslick *et al.* (47 RCTs and 16511 hypercholesterolemic participants) found a significant reduction in TG by 14% (-0.34 mmol/l (30.12 mg/dl), 95% CI: -0.41; -0.27) after an average daily dose of 3.25 g of EPA/DHA for 24 weeks [44]. These results were confirmed in normolipidemic and borderline hyperlipidemic subjects [45]. In a meta-analysis of 22 RCTs and 1366 participants with liver steatosis, ω-3 PUFAs supplementation significantly decreased liver fat (pooled risk ratio 1.52; 95% confidence interval (CI) 1.09 to 2.13), TG levels (−28.57; −40.81 to −16.33), HDL (3.55; 1.38 to 5.73), and BMI (−0.46; −0.84 to −0.08) when compared with placebo [46]. These results confirmed those obtained in the meta-analysis of He et al. (including 7 RCTs and 442 patients) in which DHA and EPA supplementation contributed significantly to the reduction of circulating levels of AST and GGT in patients with NAFLD [47]. Another meta-analysis of 4 RCTs which included 263 children showed that long-term supplementation with EPA and DHA was associated with a 25% reduction of both circulating AST and ALT levels, and the degree of steatosis assessed by liver ultrasound scan [48]. These effects are mediated by the hypotriglyceridemic and anti-inflammatory actions of EPA and DHA and suggest that these agents should be considered as effective supplements in the management of NAFLD and NASH.

3.1.3. Safety

No serious side effects have been reported with doses of EPA and DHA up to 4 g/day; most adverse events are mild gastrointestinal symptoms. However, the risk of atrial fibrillation seems to be increased as reported by recent trials including people in primary prevention, but the evidence supporting this observation is controversial [49,50]. In general, all the guidelines agree on the safety of PUFAs, despite the relatively frequent fishy aftertaste and occasional abdominal discomfort such as nausea, gastroesophageal reflux, bloating and dyspepsia [51].

3.2. Silymarin

Silymarin is an extract that includes a set of antioxidant substances extracted from milk thistle (Silybum marianum) of which the most concentrated are six flavolignans (silybin A and B, isosilybin, silidanin, silicristine and isosilicristine) and a flavonoid (taxifolin) [52]. In general, both silybin A and B represent up to 70% of silymarin extract and the most evident biological effects of silymarin could be attributed particularly to these components [53].

3.2.1. Mechanism of action

Silymarin, and/or silybins act through different mechanisms which include antioxidant, anti-inflammatory, antifibrotic and insulin sensitivity effects (Table 2). Several in vitro models (such as rat liver microsomes, human platelets, leukocytes, endothelial cells, erythrocytes, and fibroblasts) have confirmed the ability of silymarin as a potent scavenger of ROS. Moreover, silybin reduces superoxide anion radicals and nitric oxide production in the Kupffer cells [54], also improving the generation of glutathione in the liver via an increase in substrate (cysteine) availability for its biosynthesis [55]. Silymarin also possesses anti-inflammatory activities by suppressing the activity of hepatic NF-κB activation and thus the production of $TNF^{-\alpha}$, interferon-γ, IL-2 and IL-4 [56]. Silymarin modulates the inflammatory pathways through inhibition of prostaglandin E2 and leukotriene B4 formation in Kupffer cells [57].

Silymarin also acts as an antifibrotic agent and has been shown to inhibit the conversion of stellate cells into fibroblasts and to down-regulate the expression of profibrotic genes (procollagen III, transforming growth factor-beta (TGF-β)). These results have been confirmed both in an animal model of alcohol-induced hepatic fibrosis and in non-alcohol-induced hepatic fibrosis [58,59].

Silymarin appears to reduce the lipid peroxidation of LDL, acting as a chain breaking antioxidant by scavenging free radicals. Moreover, studies in vitro have shown an inhibitory effect of silybin on HMG-CoA reductase [60]. Finally, in a rat model of NAFLD, silymarin reduced visceral obesity and improved insulin resistance through inhibition of gluconeogenesis and enhancing lipolysis [61].

3.2.2. Efficacy

The available clinical evidence suggests that silymarin, administered alone or in combination with other supplements such as vitamin E, improves indirect markers of hepatosteatosis (LAP and HIS) and insulin resistance after only 3 months of treatment [62]. In a multicentre RCT, which included 180 people with histological diagnosis of NAFLD/NASH, supplementation with silybin (188 mg), vitamin E (180 mg) and phosphatidylcholine (388 mg) for 12 months determined a significant reduction of GGT activity and normalisation of transaminases levels [63]. In addition, liver steatosis was significantly decreased as measured in ultrasound scans and a second liver biopsy (in one-fifth of the patients) [67]. Moreover, silybin has been reported to improve fasting glucose and insulinemia in patients with histologically documented NAFLD [67]. This result was confirmed by a meta-analysis of 8 RCTs and 587 patients, in which silymarin supplementation reduced AST and ALT activities significantly more than the control group (AST UI/L: MD = -6.57; 95% CI, -10.03 to -3.12; p = 0.0002; ALT UI/L: MD = -9.16; 95% CI, -16.24 to -2.08; p = 0.01) [64]. The recent meta-analysis by Kalopitas et al. that included 8 RCTs confirmed these results [65]. Furthermore, in a preliminary study, the supplementation of silymarin 420 mg/day reduced the 4-year risk of mortality in patients with cirrhosis [66]. In the light of these considerations, the Mayo Clinic has classified the use of silymarin for hepatoprotection as Grade B (“Good scientific evidence for

Table 2
Hepatoprotective mechanisms of action of silymarin (modified and updated from *Cicero* et al. [31]).

Effect	Mechanism of action
Antioxidant	Direct ROS scavenger activity *Mitochondrial function optimization *Activation of protective molecules such as heat shock proteins (HSPs), thioredoxin and sirtuins
Anti-inflammatory	Inhibition of NF-kB activityProinflammatory cytokine synthesis reduction (IL-1, IL-2, IL-4, IL-6, TNF-α, TNF-β, interferon-γ, prostaglandin E2 and leukotriene B4) *
Anti-apoptotic	Slight modulation of caspase release and TNF-α effect
Antifibrotic	Inhibition of the conversion of stellate cells into fibroblastsDown-regulation of the expression of profibrotic genes (procollagen III, TGF-β)
Endocrine-metabolic	Partial activation of estrogen receptors *Insulin-sensitizing action *PPAR-agonist action *Increased expression of GLUT4 on the cell surface *Inhibition of HMG-CoA reductase *
Choleretic	Up-regulation of the bile salt export pump *

GLUT4 = glucose transporter type 4, IL = interleukin, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, PPAR = peroxisome proliferator-activated receptor, TGF-β = transforming growth factor beta, HMG-CoA = Hydroxy-Methyl-Glutaryl Coenzyme A, HSPs = heat shoch proteins, TNF = tumor necrosis factor; * potentially positive effects on vascular health.

this use") [67]. Moreover, a meta-analysis of five RCTs, which enrolled 270 type 2 diabetic patients, showed a significant effect of silymarin supplementation in improving fasting glucose (−26.86 mg/dl; 95% CI −35.42-18.30) and haemoglobin A1c (HbA1c) values (−1.07; 95% CI −1.73-0.40) [68]. However, one of the greatest limitations regarding silymarin supplementation is undoubtedly the high cost of the effective dose treatment that is required for chronic administration to have positive and permanent benefits on normalisation of the liver ultrasound scan.

3.2.3. Safety

Silymarin administration is in general well tolerated, at least in the short to medium term. However, long-term safety data is still lacking [69]. Moreover, silymarin has a very low bioaccessibility and bioavailability owing to its poor solubility. Further research is needed to improve the intestinal absorption of this extract.

3.3. Berberine

Berberine hydrochloride (BBR) quaternary ammonium salt alkaloid of the benzylisoquinoline class with a chemical formula of C20H18NO4+ and molecular mass of 336.4 units. It is naturally present in the roots, rhizomes, stems, fruits, and barks of various species of medicinal plants (in particular those of the *Berberis* genus such as Berberis aristata, Berberis vulgaris and Berberis croatica). Much is already known about the traditional uses and preparation of berberine [70]. Lipid-lowering and insulin-sensitizing actions of berberine have been extensively reported in humans [71]. Preliminary clinical data showed that these actions of BBR are related to the improvement of levels of indirect markers of hepatosteatosis (such as Hepatic Steatosis Index (HIS) and Lipid Accumulation Product (LAP)), after supplementation for 2-4 months at doses of 500 mg/day [72].

3.3.1. Mechanism of action

Berberine was the first small molecule nutraceutical that exerted a definite potential to activate LDL- receptors (LDLR) with a 3.5-fold rise in hepatic LDLR mRNA and a 2.6-fold rise in hepatic LDLR protein [73]. This led to a very wide use of berberine (generally, 500 mg/day) in hypercholesterolemia in association with monacolin K (3-10 mg/day) from red yeast rice. BBR also acts by inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), thereby reducing degradation of the hepatic LDLR and improving LDL clearance [74,75]; this mechanism has not been well assessed quantitatively. BBR may enhance the cardiovascular protection by lowering plasma cholesterol by approximately 1 mmol/L and plasma triglyceride by approximately 0.5 mmol/L [76]. In addition, BBR is an activator of AMPK, which results in an increase in fatty acid oxidation, a reduction in the expression of lipogenic genes and improved glucose metabolism. In this sense, this nutraceutical can directly regulate the expression of hepatic genes related to glucose and lipid-metabolism, thus representing a particularly interesting supplement for individuals with NAFLD. BBR could also exert antioxidant activities by inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated oxidative stress [77]. Nevertheless, it is important to emphasize that BBR is one of many bioactive molecules present in plants, suggesting the possibility of pleiotropic activities from other compounds identified in the phytocomplex, such as alkaloids, vitamins, tannins, flavonoids and flavanols, triterpenes, and coumarins [78].

The bioavailability of BBR is <1%, since it forms a self-particulate aggregation which reduces its solubility in the gastrointestinal tract; it has a low permeability and it undergoes a hepatic and intestinal first pass metabolism, being also a substrate of the efflux pump P-glycoprotein (P-gp). For these reasons, its actions are probably mainly located in the intestine. In fact, BBR has been reported to reduce the levels of lipids and glucose in the circulation while concomitantly modulating the gut microbiota composition [79]. In particular, BBR improved intestinal biodiversity (Bacteroidetes/Firmicutes ratio) with beneficial effects on the immune cells of the intestinal immune system, modulating the expression of different intestinal immune factors. BBR contributes to the inhibition of the mRNA expression of IL-1β, IL-4, IL-10, macrophage migration inhibitory factor (MIF), and TNF-α, thus decreasing the low-grade inflammation, which may exacerbate NAFLD [80]. BBR can also modify liver diseases through modulation of the intestinal flora by regulating farnesoid X receptor (FXR) and NF-κB signalling pathways, which can then mediate the metabolism of bile acids, lipids, and glucose [81]. Finally, BBR has been shown to enrich the population of butyrate-producing bacteria in the gut microbiota, thus promoting the synthesis of butyrate which can lower the levels of lipids and glucose [82].

3.3.2. Efficacy

Several studies have been conducted to evaluate both the glucose- and lipid-lowering action of BBR. *In a* meta-analysis that included 27 RCTs and 2569 participants, BBR reduced LDL-C: –0.65 mmol/l (95% CI: –0.75; –0.56, p = 0.00001) (25.14 mg/dl) and triglycerides (TG): –0.39 mmol/l (95% CI: –0.59; –0.19, p = 0.0001) (34.5 mg/dl), and increased high density lipoprotein (HDL) cholesterol: 0.07 mmol/l (95% CI: 0.04; 0.10, p = 0.00001) (2.71 mg/dl) [83]. Another meta-analysis of 6 RCTs and 501 patients, confirmed the BBR-induced benefits on lipid parameters, insulin resistance, hepatic markers, and degree of hepatic steatosis in patients with NAFLD [84]. However, these studies have used relatively high BBR doses (i.e., 1000-1500 mg/day), which may be associated with intestinal disorders.

In another RCT of 184 patients with NAFLD, BBR treatment plus lifestyle intervention resulted in a significant reduction of hepatic fat content (52.7 *vs* 36.4%, p=0.008), paralleled with greater improvements in body weight, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and serum lipid profiles (all p<0.05). Of note, BBR was more effective than pioglitazone 15 mg/day in lowering body weight and improving the lipid profile [85], while reducing transaminases as well [86] In addition, the levels of IL-6 and monocyte chemoattractant protein-1 (MCP-1) (p<0.05 for each), as well as hs-CRP, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and matrix metallopeptidase 9 (MMP-9) were decreased in BBR-treated patients [87].

Very recently a randomized controlled trial on berberine ursodeoxycholate (1 g bid) for 18 weeks vs placebo in NAFLD patients with diabetes, showed a significant reduction in liver fat content (-4.8 vs 2.0%, p=0.01) together with improved glycemic control and liver enzymes as well as weight loss[88]. This new formulation of berberine may be of choice in the treatment of advanced NAFLD with diabetes.

In summary, the use of BBR at doses ranging between 500 and 1500 mg/day has been shown to be effective in ameliorating NAFLD and related metabolic disorders. Its use can therefore be considered, especially in patients with mild hypercholesterolemia, hyperglycemia, and metabolic syndrome (MetS) associated with NAFLD [89].

3.3.3. Safety

BBR supplementation at doses up to 1 g/day is considered safe and well tolerated. Fixed dose associations with Red Yeast Rice molecules have not been linked to significant side effects. Otherwise, mild to moderate side effects are reported, mostly gastrointestinal (diarrhoea, constipation, abdominal distension) and comparable to the control groups. No significant difference was found in the levels of creatinine, AST and ALT compared with the control group [90]. The main contraindication is concern in pregnancy and breastfeeding (BBR can be transmitted to the new-born through breastfeeding). In addition, BBR could cross the placenta and might cause harm to the foetus. Finally, kernicterus, or bilirubin encephalopathy has occurred in some infants exposed to BBR: this compound seems to reduce the hepatic clearance of bilirubin [91,92]. Regarding the risk of drug interactions, this is very low in clinical practice, especially due to the low systemic

bioavailability of BBR. However, at higher doses than those commonly used as a supplement, it can increase the plasma concentration of cyclosporine [93], maybe due to a decrease in the metabolism of cyclosporin via inhibition of CYP450 (3A4) in the liver and/or intestinal wall.

3.4. Coenzyme Q10 (CoQ10)

CoQ10 is an organic molecule which can be synthesised by human cells and this shares part of the cholesterol synthetic pathway. It consists of a benzoquinone group with a poly-isoprenoid side chain (10 units in humans), and it is generally present in cell membranes and especially in the mitochondria in both its reduced (ubiquinol) and oxidized (ubiquinone) forms [94]. CoQ10 has the chemical formula of C59H90O4, a molecular mass of 863.3 units and is highly hydrophobic.

3.4.1. Mechanism of action

CoQ10 is a well-known anti-adipogenic molecule, having a positive impact on NAFLD. Nevertheless, the specific mechanisms of action are still unclear. It is possible that it acts as an anti-inflammatory and antioxidant agent by modulating the NF-κB-dependent gene expression [95]. Therefore, its deficiency could have a role in increasing the levels of inflammatory mediators such as NF-κB [96]. In addition, CoQ10 downregulates the expression of sterol regulatory element-binding protein-1c (SREBP-1c), fatty acid synthase (FAS), and acetyl-CoA carboxylase (ACC), which are well known to be related to lipid synthesis and it also modulates the expression of carnitine palmitoyltransferase-1 (CPT-1) and peroxisome proliferator-activated receptors α (PPARα), which are associated with fatty acid oxidation [97]. CoQ10 was also found to bind and activate both PPARs alpha and gamma, suggesting a key role in relaying the states of mitochondria and peroxisomes [98]. Recent studies have focused the attention on mitochondrial protein mitofusin 2 (Mfn2) that appears to protect against liver disease. In this regard, liver biopsies from NAFLD patients showed a reduction in the expression of Mfn2 [99]. This effect seems to be associated with a reduction in adenosine triphosphate ATP production due to alterations of mitochondrial respiration, and this defective oxidative phosphorylation process seems to originate from a depletion of the mitochondrial CoQ10 pool [100]. Finally, CoQ10 is an activator of AMPK, which is involved in the regulation of the hepatic lipid metabolism, limiting the abnormal accumulation of hepatic lipids, and preventing the progression of NAFLD [112].

3.4.2. Efficacy

In a RCT including 41 subjects with NAFLD, the supplementation with 100 mg/day of CoQ10 for 3 weeks resulted in a significant reduction of GGT, AST, hs-CRP, and severity of NAFLD ($p < 0.05$ for all), as well as an improvement in the adiponectin/leptin ratio ($p = 0.016$) [101]. This result confirmed the findings of another RCT, in which the same dose of CoQ10 was used in 44 NAFLD patients for 4 weeks and led to a significantly decreased waist circumference (WC), serum AST, and total antioxidant capacity ($p < 0.05$ for all) [102].

However, data regarding the reduction of adiponectin levels is still contradictory. In fact, in a study which recruited individuals with coronary artery disease, the administration of 300 mg/day of CoQ10 for 12 weeks had no significant effect on serum adiponectin levels [103]. Similar findings were demonstrated by Gokbel et al. with 100 mg/day of CoQ10 supplementation in healthy individuals [104]. Moreover, CoQ10 could help to improve the lipid pattern typically associated with NAFLD, as well as decrease oxidized-LDL levels and arterial pressure[105].

Nevertheless, the main limitation pertaining to the use of CoQ10 is its extremely low bioavailability [122]. For this reason, the need for high dosages (>100 mg/day) of pharmaceutically modified formulations with an increased bioavailability is important to enable improvements in anthropometric and biochemical variables in NAFLD.

3.4.3. Safety

CoQ10 has an excellent safety profile, and no drug interactions have been reported [106]. Moreover, it could be particularly indicated in people with NAFLD, or NASH associated with dyslipidaemia under treatment with statins [107,108]. Statins, the cornerstone of any lipid-lowering treatment, inhibit HMG-CoA reductase, a rate limiting enzyme not only in cholesterol synthesis but also in the synthesis of farnesyl pyrophosphate that is essential for CoQ10 biosynthesis, thus explaining the link between statin use and CoQ10 deficiency [109]. In fact, a meta-analysis of 12 RCTs including 1776 participants concluded that, when compared to the placebo group, statin treatment resulted in a reduction of circulating CoQ10 (SMD - 2.12; 95%CI - 3.40 to - 0.84; p= 0.001), independently from type of statin, intensity, or treatment time [110]. Another meta-analysis of 12 RCTs involving 575 patients concluded that, CoQ10 supplementation, when compared to the placebo group, ameliorated statin-associated muscle symptoms, such as muscle pain (weighted mean difference (WMD) -1.60; 95%CI -1.75 to -1.44; P<0.001), muscle weakness (WMD -2.28; 95%CI -2.79 to -1.77; P=0.006), muscle cramp (WMD -1.78; 95%CI -2.31 to -1.24; p<0.001), and muscle cramps (WMD -1.75; 95% CI -2.31 to -1.19; p<0.001) [111]. These positive effects are usually achieved only with high dosage of CoQ10 (≥200 mg/day). In addition, it has been clinically suggested that CoQ10 supplementation may improve self-perceived fatigue in healthy subjects [112], obese patients [113], and in patients affected by fibromyalgia [114,115]. These findings were, however, not confirmed in patients with statin associated myalgia, where no significant beneficial effects of CoQ10 were reported [116], even if the treatment with simvastatin and the combination of simvastatin and ezetimibe significantly decreased plasma CoQ10 levels [117].

The conflicting results of CoQ10 on muscle outcome may be explained to a multiplicity of heterogeneous factors, including the prescribed dose of this supplement (40-600 mg/day), the type of CoQ10 (ubiquinol or ubiquinone), the pharmaceutical form (e.g., powder, nano emulsion, in complex with polysorbate 80), the sample population (e.g., age, sex, comorbidities) and duration, persistence and adherence to treatment [118].

3.5. Curcumin

Curcumin is the major curcuminoid extracted from Curcuma longa with well-known anti-inflammatory and insulin-sensitizing actions [119,120]. The chemical formula is C21H20O6, and the molecular mass is 368.38 units, and the compound has an intense yellow-orange colour and is insoluble in water. Several preclinical and clinical studies suggest a possible role of this supplement in individuals with NAFLD or NASH [121,122].

3.5.1. Mechanism of action

Curcumin may have a beneficial role in mitigating NASH development through its anti-inflammatory actions, exerted via modulation of several transcription factors, including NF-κB, PPAR$^{-\gamma}$, p53, and carbohydrate response element-binding protein (ChREBP) [123]. In addition, curcumin suppresses growth factors, cell proliferation factors and inflammatory cytokines, such as TNF-α, interleukins (IL-1 and IL-6) and cyclooxygenase-2 (COX-2) [124]. However, even though curcumin is known to have a variety of biological effects, the underlying mechanisms of its effect on NAFLD are still largely unknown. An interesting field of research is the study of changes in the gut microbiome after curcumin supplementation, as well as its effect on intestinal barrier function, which, if altered, is associated with a major risk of low-grade chronic inflammation and the risk of steatohepatitis [125]. In this regard, curcumin showed similar effects to metformin in alleviating hepatic steatosis, improving intestinal barrier integrity, reducing the Firmicutes/Bacteroidetes ratio and modulating gut microbiota in high-fat diet-induced obesity rats with NAFLD [126].

3.5.2. Efficacy

In a recent RCT, 80 patients with NAFLD treated with curcumin (250 mg/day) for 2 months benefited from a reduction in the grade of hepatic steatosis and serum AST levels ($p=0.015$ and $p=0.007$, respectively, when compared to the placebo) [127]. In another RCT of 45 obese women with NAFLD, treatment with curcumin in combination with resistance training led to a significant reduction of both AST and ALT levels ($p\leq0.05$) when compared with the baseline values [128]. Meta-analyses by Goodarzi et al. [129] and Wei et al. [130] suggest that turmeric/curcumin may have a favourable impact on serum transaminases and insulin sensitivity in NAFLD patients. In accordance with these results, a meta-analysis of 9 RCTs found that curcumin supplementation (50-1500 mg/day) improved both metabolic markers and anthropometric parameters with a significant reduction in ALT and AST levels, serum total cholesterol, LDL-C, fasting blood glucose, HOMA-IR, serum insulin and waist circumference[131]. The positive effects of curcumin supplementation on visceral fat and abdominal obesity have also been reported in another meta-analysis of 8 RCTs and 520 participants with NAFLD. Curcumin at dosages ranging from 70-3000 mg/day administered for 8-12 weeks significantly reduced BMI (WMD = -0.34 kg/m2, 95% CI [-0.64, -0.04], $p<0.05$) and waist circumference (-2.12 cm, 95% CI [-3.26, -0.98], $p<0.001$)[132]. Another study including 100 Asian patients with NAFLD and metabolic syndrome, showed that NAFLD histological features were improved after a daily administration of 400 mg of curcumin, confirmed by liver ultrasound [133]. However, it is important to highlight that the most promising results were observed with high and bioavailable dosages of curcumin. In this context, a RCT of 102 Iranian patients with NAFLD treated with phytosomal curcumin, 500 mg b.i.d. for 8 weeks, showed a significant reduction in transaminase LEVELS, waist circumference and BMI, but especially in the degree of hepatic steatosis in 75% of the treated population [134]. Curcumin administration elicits pleiotropic activities, including the reduction of serum uric acid ($p<0.001$) [135] and raised adiponectin (+76.78%, $p=0.033$) levels [136]. Finally, curcumin use is also associated with an improvement in FMD [137] and in patients with DM2 pulse wave velocity (PWV) [138]. Nevertheless, the usually high dosages of pure and bioavailable curcumin (i.e., >1000 mg/day) needed to improve NAFLD may reduce adherence to treatment due, in part, to the high costs of the pharmaceutical techniques required to achieve high bioavailability. In recent years, new pharmaceutical formulations, such as phospholipid curcumin, have been developed to increase the solubility of this molecule, reduce dosage, and thus improve adherence.

3.5.3. Safety

The safety profile of curcumin is long established and very well documented. According to the Joint United Nations and World Health Organization Expert Committee on Food Additives (JECFA) and EFSA reports, the Allowable Daily Intake (ADI) level of curcumin is 0-3 mg/kg body weight [139]. Even though curcumin is considered safe and well tolerated, some mild and transient side effects have been reported, including diarrhoea, headache, rash, yellow stool and reversible increases in alkaline phosphatase and lactate dehydrogenase [140]. However, most of them might be since some producers, to increase the curcumin bioavailability, add piperine, which might cause some of the abovementioned side effects.

3.6. Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a non-flavonoid phenol, particularly concentrated in grape skin peel, but also in the extracts of Polygonum cuspidatum, commonly known as Japanese knotweed. It has poor oral bioavailability (if not chemically modified), exerting important antioxidant and vasoprotective activities (both in the cerebral and peripheral circulation) [141,142]. Its relatively high concentration in red wine may explain, at least in part, the relatively low incidence of CVD in the French population, despite the prevalence of a high-fat diet consumption [143]. Resveratrol with the chemical formula C14H12O3 and molecular mass of 228.24 units is a relatively thermally stable compound that could be obtained in bulk from the wine industry [144]. Although resveratrol may not be stable during storage, its association with other compounds can enhance shelf-life [145].

3.6.1. Mechanism of action

Resveratrol has antioxidant properties through the reduction of reactive oxygen species (ROS) $^{\text{and RNS}}$ (reactive nitrogen species) production, improvement in endogenous antioxidant enzyme activity (e.g., superoxide dismutase (SOD), catalase (CAT), glutathione (GSH)) and elimination of direct free radicals [146]. Resveratrol indirectly induces autophagy through an mTOR-dependent (target of rapamycin in mammals) or TFEB-dependent (EB transcription factor) pathway via the AMPK (AMP-activated kinase)/SIRT1 (sirtuin 1)/Nrf2 (nuclear factor 2), ERK/p38 (signal-regulated extracellular kinase), MAPK (mitogen-activated protein kinase), and PTEN/Akt (phosphatase and tensin homolog/protein kinase B) signalling pathways, thus promoting the synthesis of antioxidant molecules and the expression of respective genes [147]. In addition, resveratrol acts by inhibiting the erythroid Nrf2 ubiquitination, safeguarding its functionality, which also includes the transcription of antioxidant genes such as SOD and CAT [148].

The antioxidant activity of resveratrol plays a role in the reduction of liver fibrosis progression and infiltration of inflammatory cells, representing a typical feature of NAFLD [149]. This reduction of the inflammatory molecules and malondialdehyde (MDA) levels seems to be associated, in part, with the inhibition of mRNA expression of inflammatory mediators - such as inducible nitric oxide (NO), TNF-α (tumour necrosis factor-α), and IL-1β (interleukin-1β) [150]. However, an important pathway of action is the activation of the AMPK/SIRT1 axis, which reduces the accumulation of hepatic fat via increased oxidation of fatty acids and reductions in lipogenesis [151]. In this context, the activation of SIRT1 and AMPK improves metabolic lipid homeostasis [152].

3.6.2. Efficacy

Even though several studies *in vitro* and pre-clinical data suggest that resveratrol could be considered as an anti-NAFLD agent, preliminary clinical data appear to contradict preclinical literature [153]. These contrasting results may be in part explained because RCTs conducted to date were for a major part of too short duration to have an impact on the liver structure and with resveratrol doses unable to confer the insulin-sensitizing action that could improve NAFLD. In fact, in a 3-month study, which included overweight or obese people with NAFLD, 150 mg/day of resveratrol had no effect on liver fat content or cardio-metabolic markers [154]. However, when used at the appropriate dose (i.e., >150 mg/day) and for long periods, resveratrol has already been shown to exert an antihypertensive effect in those affected by NAFLD [155]. A recent meta-analysis of 6 RCTs showed that resveratrol supplementation significantly reduced levels of TNF-α (SMD = -0.46; 95% CI (-0.78, 0.14); $p= 0.005$) and high sensitivity C-reactive protein (hs-CRP) (SMD = -0.53; 95% CI (-1.01, -0.05); $p= 0.030$), although no other significant changes were observed for markers of insulin sensitivity, glucose and lipid profile or hepatic steatosis [156]. Similar conclusions were reached in another meta-analysis of 7 RCTs, including 302 patients with NAFLD. In this regard, the supplementation of resveratrol in doses ranging from 500 to 3000 mg/day, for periods between 56 and 180 days, did not affect the parameters of hepatic steatosis or the glucose/lipid profile ($p < 0.05$) [157].

Contrasting results were shown with a micronized formulation of trans-resveratrol. In this context, the supplementation of micronized formulation of trans-resveratrol in NAFLD patients demonstrated promising results for the treatment of this condition through the reduction of liver fat, aspartate aminotransferase (AST), alanine aminotransferase, GGT (gamma-glutamyl transferase) and insulin resistance [158]. This study highlights the need for new long-term RCTs

conducted in individuals with NAFLD and with the use of highly bioavailable resveratrol, as liver macro-modification is likely to require long-term high-dose/good-bioavailability resveratrol treatment.

3.6.3. Safety

No serious adverse reactions associated with resveratrol were reported during the studies, even at high doses (1000 mg/day) [159]. However, at doses of ≥2.5 g/day, side effects may occur, such as nausea, vomiting, diarrhoea, and liver dysfunction in patients with NAFLD [160]. No major side effects were reported in long-term clinical trials [161].

3.7. Green tea

Green tea is a natural source of polyphenolic compounds and, in particular, (−)-epicatechin-3-gallate, (−)-epigallocatechin (EGC) and (−)-epicatechin. The (−)-epigallocatechin-3-gallate (EGCG) demonstrates the strongest antioxidant and anti-inflammatory properties [162], with potential positive effects on NAFLD and CVD.

3.7.1. Mechanism of action

Green tea is particularly rich in antioxidants such as polyphenols (up to 35% of dried weight), which are protective against CVD and potentially in people with NAFLD. It has been suggested that polyphenols from green tea act through the reduction of the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), inhibiting both inflammation and oxidative stress, and thus, potentially NAFLD progression [163]. Green tea also increases the circulating level of adiponectin, which has strong anti-inflammatory and antioxidant effects, antagonizing the actions of TNF-α, decreasing the proliferation of hepatic satellite cells, and increasing apoptosis [164]. In addition, flavan-3-ols were shown to reduce lipid peroxidation, interfere with micellar solubilization and absorption of cholesterol, activate the AMPK (thus, stimulating lipogenesis and improving glucose homeostasis) and inhibit the key enzyme in the synthesis of cholesterol, hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase [165]. Lastly, tea catechins inhibit the ileal apical sodium-dependent bile acid transporter, decreasing reabsorption of bile acids and thus improving the biliary excretion of cholesterol [166].

3.7.2. Efficacy

Although multiple RCTs have investigated the effects of green tea, catechin, and other forms of green tea supplementation on blood markers of liver function, the results of these studies have been inconsistent [167,168,169,170]. This heterogeneity may be explained by the fact that in most RCTs the extracts of green tea were not standardised, and the period of treatment was too short to see changes in clinically relevant outcomes.

A meta-analysis of 15 RCTs demonstrated a non-significant effect of green tea supplementation on liver enzymes (ALT [SMD= -0.17, CI -0.42 to 0.08, p = 0.19], AST [SMD = -0.07, CI -0.43 to 0.29, p = 0.69], alkaline phosphatase (ALP) [SMD = -0.17, CI -0.45 to 0.1, p = 0.22]) and bilirubin levels. However, subgroup analyses showed that green tea intake reduced the levels of liver enzymes in people with NAFLD [171]. This result may suggest the variability of the antioxidant effect of catechins from green tea, depending on the oxidative status of individuals as confirmed by other studies. In fact, in people with high baseline oxidative stress, green tea seems to reduce ROS concentration, while in those at low baseline oxidative stress, this extract led to ROS production [172].

Another meta-analysis of four RCTs, including only NAFLD patients treated with green tea extract or control, showed a reduction in ALT (-12.81 U/L; 95% CI: -18.17 to -7.45) and AST (-10.91 U/L; 95% CI: -19.66 to -2.17) blood levels. In addition, a favourable effect of green tea administration was observed on body mass index (BMI), triacylglycerol, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) [173]. This data confirmed results obtained by a meta-analysis of 20 RCTs with 1536 participants, which showed a reduction of LDL-C (mean difference (MD): –0.19 mmol/l (7.35 mg/dl); 95% CI: –0.3; –0.09, p= 0.0004) with tested daily doses ranging from 250 to 1200 mg of green tea extract or from 170 to 850 mg of EGCG [174]. Green tea consumption is also associated with an improvement in flow mediated dilatation (FMD) [175] and pulse wave velocity (PWV) [176] and may be associated with a decreased risk of CVD morbidity and mortality [177].

3.7.3. Safety

Usually, the consumption of green tea is well tolerated, however, in some cases rash, transient elevation of blood pressure (probably owing to the presence of caffeine) and mild gastrointestinal disorders may occur [178]. Some cases of hepatic injury caused by green tea have been reported in the literature, especially in women. Therefore, a gender-dependent green tea hepatotoxicity may exist. The hepatotoxicity is probably due to EGCG or its metabolites, which may induce oxidative stress in the liver. In some cases, toxicity related to concomitant medications may be implicated [179]. High doses of green tea can cause a deficiency of iron and folate due to its capacity to bind and reduce their intestinal absorption. Therefore, particular attention should be given to green tea consumption during pregnancy [180]. Detrimental effects of overconsumption of green tea have been ascribed to the presence of aluminium [181].

3.8. Artichoke

Artichoke (*Cynara scolymus, Cynara cardunculus*) is a vegetable widely consumed as part of a traditional Mediterranean diet [182], constituting a source of antioxidants such as mono-caffeoylquinic acid and dicaffeoylquinic acid (cynarine and chlorogenic acid), caffeic acid (1%) and the volatile sesquiterpenes and flavonoids (1%) (including the glycosides luteolin-7–β-rutinoside, luteolin-7–β-glucoside and luteolin-4–β-D-glucoside). In this context, artichoke leaf extract has shown potential as a lipid-lowering agent in patients with mild hypercholesterolemia, with a robust HDL-C increasing effect [183].

3.8.1. Mechanism of action

Artichoke leaf extract exerts a lipid-lowering activity by the inhibition of HMG-CoA reductase and acetyl-CoA C-acetyltransferase (elicited by artichoke flavonoids), in addition to increased faecal excretion of bile salts [184]. Moreover, artichoke modulates SREBPs in the liver (which are paradoxically elevated in patients with NASH). The lipid-lowering activity of artichoke can positively affect the hepatic indices, which are generally altered in the phenotype of NAFLD patients with hypertriglyceridemia [185]. Studies conducted with a preparation of Jerusalem artichoke revealed further mechanisms of action. For example, study in high-fructose diet-fed rats showed that artichoke leaf extract improved the gene expression of decorin (related to fibrosis), malic enzyme 1 (associated with fatty acid synthesis) and nicotinamide phosphoribosyltransferase (related to inflammation) [186].

3.8.2. Efficacy

The lipid-lowering effect of artichoke leaf extract has been reported in several RCTs, albeit with contrasting results. In one RCT, 75 hypercholesterolemic adults treated for 12 weeks with 1280 mg/day of artichoke extract showed a mean reduction of total cholesterol by 4.2% (when compared with baseline), whereas no significant difference between groups was observed for LDL-C levels [187]. However, in a meta-analysis of nine RCTs including 702 dyslipidemic subjects, a significant reduction in plasma concentrations of total cholesterol (p=0.001), LDL-C (p=0.011) and TG (p=0.011) was observed. Subgroup analysis showed that artichoke could decrease total cholesterol, LDL-C and TG in people with high baseline values but not in those with normal baseline levels. In addition, artichoke extracts exerted pleiotropic activities by improving AST and ALT (p<0.001), fasting blood glucose (p=0.029), and systolic blood pressure (p=0.004) [188]. In

another RCT, 60 patients with dyslipidemia and NASH were treated with 2700 mg/day of artichoke extract or placebo for 2 months. At the end of the treatment, LDL-C was significantly reduced by 11.5% (p=0.039) and TG by 20.1% (p=0.011) when compared with baseline [189]. Furthermore, there were significant decreases in the serum AST and ALT levels compared with the placebo group (p<0,001).

3.8.3. Safety

No serious adverse events have been reported in any of these studies, confirming the excellent safety profile of artichoke leaf extracts. This supplement could also be used in statin-intolerant individuals [190], for its hepatoprotective activity, which is demonstrated by its reduction of elevated serum ALT activity. A few cases of minor and transient gastrointestinal effects (mainly abdominal discomfort) have been reported [191]. Even though the artichoke leaf extract could represent an adjuvant in the regulation of lipid profile and liver levels of AST and ALT in NAFLD patients, long-term RCTs are still missing and needed to confirm both the safety and efficacy of this nutraceutical.

3.9. Vitamin E

Vitamin E consists of a group of eight lipophilic molecules synthesized by plants starting from homogentisic acid. As a nutraceutical, vitamin E has been tested in individuals with NAFLD, although, almost always, in association with silymarin. The term "vitamin E" encompasses four tocopherols (alpha (α), beta (β), gamma (γ), and delta (δ), the saturated forms) and four tocotrienols (α, β, γ, δ, the unsaturated forms) [192]. Currently, the most studied form of vitamin E is the synthetic one, which consists prevalently of α-tocopherol in a racemic mixture of eight stereoisomers (2RS, 4'RS, 8'RS) [193]. α-Tocopherol also occurs in the common food oils, including corn, peanut, and soybean oil [194].

3.9.1. Mechanism of action

Vitamin E potentially exerts anti-atherogenic and anti-inflammatory activities in addition to being a well-known antioxidant [195]. The ability of vitamin E to scavenge free radicals is not limited to ROS but it also acts against reactive nitrogen species [196]. Vitamin E supplementation in murine animal models has been reported to increase hepatic glutathione, improve SOD levels, reduce steatosis, inflammation, hepatic stellate cell activation, collagen mRNA expression, and to ameliorate fibrosis [197].

The anti-inflammatory effects of vitamin E could be associated with its ability to modulate the expression of the fibrotic genes TGF-β, MMP-2 and NF-κB, inflammatory factor COX-2, and pro-apoptotic genes (*Bax*) [198]. Furthermore, α- or γ-tocopherol exert a hepatoprotective role in an obese mouse model by suppressing hepatic malondialdehyde, TNF-α, IL-1, IL-2, IL-4, IL-6, and IL-8 and serum ALT levels [199], in addition to improving the integrity of the liver by down-regulating hepatic cluster of differentiation 36 protein (CD36), a membrane transporter responsible for the uptake of fatty acids into the liver in a guinea pig model [200].

3.9.2. Efficacy

Several clinical trials have been conducted to assess the efficacy of vitamin E in NAFLD or NASH. In general, supplementation with 100-1200 IU/day of vitamin E for at least 24 weeks can improve liver biochemistries and histology [201]. The combination of ursodeoxycholic acid with vitamin E can further improve steatosis and transaminase levels when compared with conventional therapy alone [202]. In addition, an improvement in histological lesions was observed in patients with NASH [203].

In the PIVENS (Pioglitazone, Vitamin E or Placebo for Nonalcoholic Steatohepatitis) trial, patients with NASH treated with high-dose vitamin E (800 IU/day) for 96 weeks showed a reduction in hepatocyte ballooning (50 vs 29%, p = 0.005) and lobular inflammation (54 vs 35%, p = 0.02), in addition to an improvement in liver steatosis and ALT levels [204]. Similar results were obtained by Lavine et al. in the TONIC (Treatment of NAFLD in Children) trial, which involved 173 children that received metformin (500 mg twice daily), vitamin E (400 IU twice daily), or placebo twice daily for 96 weeks [205]. In this regard, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines consider vitamin E as a potential short-term treatment for non-diabetic adults with biopsy-proven NASH [206].

In a meta-analysis of 7 RCTs (303 adults), the long-term administration of low-dose vitamin E significantly lowered the risk of myocardial infarction (RR 0.82; 95%CI, 0.70-0.96; *p*=0.01) [207].

3.9.3. Safety

Long-term safety of vitamin E supplementation in people with NAFLD or NASH should be considered before initiating therapy. Dosages ≥400 IU/day may be associated with an increased risk of mortality as highlighted by the meta-analysis of Miller and colleagues (35,967 participants in 19 clinical trials), where, however, the data regarding the association of vitamin E with vitamin A, associated with a low mortality risk, were excluded, and comorbidities, risk factors (e.g., smoking) or the co-administration of other drugs were not considered [208]. On the other hand, a large meta-analysis of 57 trials (246,371 subjects) showed that vitamin E supplementation appears to have no effect on all-cause mortality at doses up to 5500 IU/day [209].

Vitamin E may also be related to a decreased (by 10%) RR of ischemic stroke, whereas RR of haemorrhagic stroke seems to increase by 22% (1.00 to 1.48, p=0.045) as highlighted by a meta-analysis of RCTs (118,765 healthy participants) [210]. The risk of prostate cancer may also increase slightly after vitamin E use as reported by the Selenium and Vitamin E Cancer Prevention Trial (SELECT) which included 8737 healthy subjects treated for 7-12 years with vitamin E (400 IU/day of all rac-α-tocopheryl acetate). Compared with the placebo in which 529 men developed prostate cancer, 620 men in the vitamin E group developed prostate cancer (hazard ratio [HR], 1.17; 99% CI, 1.004-1.36, p=0.008) [211]. For this reason, vitamin E supplementation should be further investigated to fully clarify the risk/benefit ratio and potential use on NAFLD and NASH.

3.10. Vitamin D

Vitamin D is an essential nutrient, secosteroid hormone, which plays a fundamental role in calcium homeostasis and mineral metabolism. Approximately 10% of vitamin D is obtained from the diet, whereas 90% is produced by the cutaneous conversion of 7-dehydrocholesterol present in the skin to cholecalciferol, a process which requires exposure to ultraviolet light B (UVB). The 7-dehydrocholesterol is then hydroxylated from the liver by a 25-hydroxylase and then from the kidney, resulting in 1,25-hydroxy-cholecalciferol (calcitriol). In recent years, epidemiological data highlighted the potential function of this molecule beyond the calcium homeostasis, suggesting a possible role in NAFLD [212].

3.10.1. Mechanism of action

This hormone possesses a wide range of pleiotropic activities (including the regulation of cell differentiation, inflammation, immune response, and gut microbiota), suggesting important actions on CV and liver health. Table 3 summarizes the pathophysiological mechanisms that link vitamin D and NAFLD. The different pathways of vitamin D actions can be modulated via the interaction of this compound with its nuclear receptor (VDR) and the subsequent heterodimerization of the ligand activated VDR with the retinoid-X-receptor (RXR), that cause a transcriptional activation or repression of different target genes through binding to vitamin D response elements (VDREs) in their promoter region [213]. In particular, calcitriol can affect the transcriptional regulation of the proliferation and differentiation of immune cells, including the Toll-like receptors (TLR)2, TLR4 and TLR9, all involved in the pathogenesis of NAFLD. In this context, vitamin D deficiency may exacerbate the progression of NAFLD by the activation of TLR2 and

Table 3
Pathophysiological mechanisms linking vitamin D and NAFLD (Modified and updated from *Cicero* et al. [31]).

Mechanism proposed	Support test	References
Insulin-sensitivity improvement	• Mice lacking vitamin D receptors are insulin-resistant • Vitamin D modulates the transcription of the insulin gene • Vitamin D deficiency worsens the secretory response of beta-cells in response to carbohydrate loading • Vitamin D improves glucose transport in muscle cells • Vitamin D up-regulates the translocation of GLUT4 and the use of glucose by adipocytes	[219,220]
Reduction of adipose tissue inflammation	• Higher levels of liver vitamin D are associated with higher levels of adiponectin • In animal models, vitamin D supplementation reduces the amount of IL-6 in adipocytes • Treatment of human adipocytes with vitamin D inhibits NF-κB and reduces the release of proinflammatory cytokines • Vitamin D inhibits the chemotaxis of macrophages and increases the expression of adiponectin in preadipocytes	[221,222,223]
Reduction of hepatic inflammation	• Vitamin D deficiency triggers Toll receptors and reduces liver inflammation • Artificial lighting in rats reduces the degree of inflammation and hepatic apoptosis • The expression of the vitamin D receptor on cholangiocytes is inversely proportional to the severity of steatosis and NAFLD scores	[224,225]
Inhibition of liver fibrosis	• Vitamin D inhibits the proliferation of hepatic stellate cells *in vitro* • Vitamin D reduces pro-fibrotic marker levels (as TIMP-1) and the production of type I collagen in cell cultures of hepatic stellate cells • Vitamin D receptor knockout mice spontaneously develop hepatic fibrosis	[226]

GLUT4 = glucose transporter type 4, IL = interleukin, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, TIMP-1 = tissue inhibitor of metalloproteinases-1

TLR4 and stimulation of inflammatory signalling molecules, thus causing steatosis and inflammation [214]. In this regard, in animal models, vitamin D deficiency correlated with raised levels of mRNA of TLR-2, TLR-4, and TLR-9, resistin, IL-4, IL-6 and expression of inflammatory genes such as TNF-α and TGF-P[215]. Vitamin D has also a positive impact on the improvement of pancreatic β-cell function, thus reducing insulin resistance, one of the major risk factors of NAFLD[216].

Moreover, vitamin D could act through the activation of phosphatidylinositol-3 kinase (PI3K) and thus the generation of secondary messengers, such as the cyclic adenosine monophosphate (cAMP) and Ca2+, as well as the modulation of other protein kinases, including protein kinases A and C, Ca2+-calmodulin kinase, and MAPK [217]. Vitamin D may ameliorate hepatic steatosis by inducing autophagy by upregulating autophagy-related 16-like 1 (ATG16L1)[218].

3.10.2. Efficacy

Recent epidemiological data suggest that individuals with NAFLD may be more frequently deficient in vitamin D when compared to the general population and that there is an inverse correlation between the severity of NAFLD and circulating vitamin D levels [227,228,229]. However, other studies are not in agreement: in a meta-analysis of observational studies including 974 people with NAFLD, no significant differences in vitamin D levels among NAFLD patients with high NAFLD activity score (NAS) *vs* low NAS (MD = −0.93, 95% CI −2.45 to 0.58) and high *vs* low fibrosis score (MD = 0.88, 95% CI −2.65 to 4.42) was observed [230]. Similar conclusions were shown by Barchetta et al. where 2000 UI/day of vitamin D supplementation, for 24 weeks, neither affected hepatic steatosis nor metabolic/CV parameters in diabetic patients with NAFLD [231].

Nevertheless, other clinical trials reported that vitamin D administration improves insulin resistance and glucose metabolism in people with NAFLD [232,233], suggesting positive implications in CV prevention. In fact, vitamin D deficiency could also be correlated with an increased risk of hypertension, vascular ageing, and high levels of hs-CRP [234,235]. *Moreover, a positive linear association* was observed between vitamin D and adiponectin levels [236]. For this reason, even though long-term RCTs on the utility of vitamin D supplementation in people with NAFLD are still missing, its integration may be considered and justified for the positive effect in CV prevention and the virtual absence of any side effects [237,238].

3.10.3. Safety

Vitamin D supplementation is generally safe and well tolerated. The upper limit of a safe dose of vitamin D may differ depending on several factors, such as gender, age, vitamin D plasma levels, dose of administration and regimen, formulation, and outcomes. Overall, the prevention or correction of vitamin D deficiency/insufficiency with 1000-2000 IU/daily of vitamin D is considered safe [239].

3.11. Probiotics and prebiotics

Several studies have reported a beneficial role of the commensal microbiota in maintaining liver homeostasis and preventing liver fibrosis in mice [240]. In this context, an imbalance of the endogenous microbiota, also known as dysbiosis, has been related to a range of chronic extra-intestinal conditions, including NAFLD, NASH and alcoholic liver disease (ALD) [241]. The discovery of a "gut-liver axis" which permit a bidirectional association between the gut and the liver is the basis of new research into probiotic treatments in patients with liver diseases and central nervous system (CNS) diseases [242].

3.11.1. Mechanism of action

How the gut microbiota influences the pathogenesis of NAFLD, or NASH is still under investigation. However, several potential mechanisms have been proposed, including the correlation between dysbiosis, and increased intestinal permeability ("leaky gut"), the reduction of the production of short chain fatty acids (SCFAs) and the alteration of bile acid and choline metabolism [243]. In particular, intestinal dysbiosis correlates with a dysregulation of gut endothelial barrier function, with enhanced intestinal permeability to microbes and/or microbial products (endotoxins, lipopolysaccharide (LPS), peptidoglycan), that can then reach the circulation through the portal system and increase the risk of inflammation and fibrosis [244].

Intestinal dysbiotic bacteria or their metabolites are thus important mediators of liver inflammation and fibrosis, acting by binding to receptors of the innate immune system (Toll-like receptors (TLRs) on Kupffer cells and hepatic stellate) on liver cells, with consequent activation of inflammatory cytokines, such as TNF-α, IL-1β and interferons. Among the TLRs family, TLR2, TRL4, TRL5 and TRL9 are implicated in the pathogenesis of NAFLD via binding LPS and activating the NF-κB pathway [245,246].

3.11.2. Efficacy

Growing evidence suggests that supplementation with both probiotics and/or symbiotics could improve several parameters related to NAFLD (e.g., insulin resistance, plasma levels of transaminases, degree of liver fat infiltration), but the available studies have been conducted with a range of different probiotic strains and therefore the results are inconsistent [247].

Hepatic steatosis has been associated with a reduction in the

biodiversity of the gut microbiota and with an increase of the *Firmicutes/Bacteroidetes* ratio [248]. In a study by Raman et al. which included 30 people with NAFLD, an increase in *Lactobacillaceae, Lachnospiraceae* and *Veillonellaceae* and a decrease in *Ruminococcaceae* were observed [249]. In addition, in NASH adult patients, *Bacteroidetes* were reduced when compared to healthy controls [250]. In contrast, Zhu et al. found increased Bacteroidetes in children with NASH [251]. Furthermore, Boursier et al. showed an abundance of Bacteroidetes in individuals with NASH, whereas the abundance of Prevotella was lower [252].

Treatment with *L. bulgaris* or *S. thermophilus* was effective in reducing the levels of ALT, AST and γ-glutamyl transferase (γ-GT) in NAFLD patients [253]. In obese children with NAFLD, supplementation with *L. rhamnosus* strain GG resulted in a significant improvement in liver function and a decrease in ALT levels [254]. Alisi et al. found a significant improvement in the severity of NAFLD (assessed by ultrasound) and a significant decrease of BMI in children with NAFLD treated for 4 months with *bifidobacteria*, *lactobacilli* and *S. thermophilus* strains [255], thus suggesting that probiotics could reduce liver fat and thus prevent the progression of NAFLD. Similar results were obtained with the consumption of 300 g/day of probiotic yogurt containing *L. acidophilus* La5 and *B. lactis* Bb12 for 8 weeks in adult patients with NAFLD; at the end of treatment, there was a significant improvement in ALT, ASP, total cholesterol, and LDL-C when compared to the control group which consumed 300 g/day of conventional yogurt [256]. In another study, including 58 people with T2DM and NAFLD, the supplementation with a multi-strain probiotic (14 probiotic bacteria genera *Bifidobacterium, Lactobacillus, Lactococcus, Propionibacterium*) significantly decreased the fatty liver index, aminotransferase levels, as well as TNF-α and IL-6 levels [257]. Moreover, in a RCT with 39 liver biopsy-proven NAFLD patients, oral daily administration of a multistrain probiotic (containing 675 billion bacteria) was shown to improve NAS score ($p = 0.004$), hepatocyte ballooning ($p = 0.05$) and hepatic fibrosis ($p = 0.018$) when compared to the placebo group [258].

The co-administration of prebiotics (oligofructose, psyllium and inulin) could improve NAFLD parameters, including levels of transaminases, TG and LDL-C, glucose metabolism and insulin resistance, as well as the grade of steatosis [259]. Alisi et al. also evaluated glucagon-like peptide 1 (GLP-1) levels (a peptide secreted by the cells of the small intestine and proximal colon), whose physiological activity is responsible of the activation of catabolism through an increase in insulin secretion and suppression of glucagon secretion [260]. The investigators showed that circulating levels of the active forms of GLP-1 were significantly higher in children with NAFLD after 4 months of symbiotic treatment (VSL#3 treatment). Although data are still inconclusive, the consumption of probiotics can improve the effectiveness of lifestyle modifications in obese individuals with NAFLD, as well as conventional liver function tests and lipid peroxidation markers [261,262] and intrahepatic triglyceride content (IHTG), as measured by proton-magnetic resonance spectroscopy [263]. The improvement in liver function may be, at least partly, due to a lower metabolic endotoxemia in the host.

3.11.3. Safety

Probiotics and prebiotics are generally safe and well tolerated with rare side effects. The Agency for Healthcare Research and Quality concluded that the existing RCTs regarding probiotic administration in humans revealed no evidence of safety issues [264].

3.12. Astaxanthin

Astaxanthin is an antioxidant molecule of marine origin with a chemical formula of C40H52O4 and a molecular mass of 594.84 units. It is a carotenoid from Haematococcus pluvialis, which can contain 1.5-3.0% of this compound that imparts a purplish red colour. Its antioxidant activity is considered more powerful compared with that of commonly used antioxidants, such as resveratrol, lycopene or vitamins A, C and E [265].

3.12.1. Mechanism of action

Ni et al. found that astaxanthin significantly reduced the release of inflammatory factors that play a crucial role in the pathogenesis of NAFLD. Indeed, astaxanthin reduces the hepatic recruitment of CD4+, CD8+ and M1 macrophages. Astaxanthin has also been demonstrated to inhibit lipid accumulation in the liver, improve insulin signal transduction and modulate pro-inflammatory pathways by suppressing the activation of Jun N-terminal kinase (JNK)/p38 mitogen-activated protein kinase (MAPK) and NF-κB pathways [266]. In a pre-clinical study involving obese mice, astaxanthin decreased macrophage infiltration and the expression of macrophage markers, thus inhibiting both fibrosis and inflammation processes in the liver and adipose tissue, as well as enhanced the ability of skeletal muscle to oxidize mitochondrial fatty acids [267]. The anti-inflammatory activity may also be attributed to its capacity to activate PPAR-α and inhibit the expression of PPAR-γ and to reduce IL-6 and TNF-α in the liver [268]. Finally, astaxanthin acts as an antioxidant agent, by increasing the activity of SOD, CAT, and glutathione peroxidase (GPx) and increasing the amount of the reduced form of glutathione (GSH) in the liver and significantly reducing lipid peroxidation [269]. In apolipoprotein E knockout mice, astaxanthin significantly reduced TG hepatic accumulation and enhanced the expression of Nrf2 target genes, such as SOD and GPx [270].

3.12.2. Efficacy

In pre-clinical experimental models, astaxanthin was more effective than vitamin E in improving insulin resistance, hepatic inflammation, lipogenesis and fibrogenesis. Thus, it appears to be the ideal natural antioxidant for the prevention of liver injury induced by NAFLD [271]. However, direct evidence of these promising data on humans is still lacking. In a RCT which included overweight and obese adults in Korea, the supplementation of astaxanthin (5-20 mg/day for 3 weeks) resulted in significant improvements of oxidative stress markers MDA, isoprostane (ISP), SOD and total antioxidant capacity (TAC) [272]. Long-term RCTs in people with NAFLD are needed before making definitive conclusions.

3.12.3. Safety

Astaxanthin is widely used in various fields due to its several biological activities and it has a good safety profile. In 1997, astaxanthin was shown to be non-genotoxic [273]. A study conducted in rats confirmed that the highest dose of 6000 mg/kg/day, did not lead to acute deaths in animals [274]. In addition, no observed adverse effect for 1000 mg/kg/day of astaxanthin supplementation for 13 weeks has been reported [275]. Similar conclusions were reached in a human study in which 20 mg/day of astaxanthin were given in 127 individuals for 4 weeks with no safety signals observed [276].

3.13. Other nutraceuticals

We also would like to emphasize that there are also other nutraceuticals that do not have still enough data confirming their efficacy and safety (to be independently presented in this Position Paper), however available reports suggest a potential beneficial application in NAFLD patients.

A meta-analysis of 8 RCTs which included 800 Asian NAFLD patients found that the dry extract of Salvia miltiorrhiza (red or **Chinese sage**, Darshan) supplementation in individuals with hepatic steatosis significantly decreased plasma transaminase levels and increased the CT contrast between liver and spleen, indicative of a reduction in the degree of hepatosteatosis [277]. However, despite the interest in this evidence, RCTs on Caucasians are currently lacking. Similar results were obtained in a preliminary experimental study with chia (*Salvia hispanica*) supplementation. In this context, 25 g/day of milled chia supplemented in individuals with NAFLD reduced the grade of steatosis by 52% ($p<0.05$),

as well as body weight, circulating free fatty acids, total cholesterol, and non-HDL cholesterol [278].

Another interesting supplement is **cardamom** (Elettaria cardamomum), a member of the ginger family, commonly known as "the queen of spices" since it consists of several polyphenols, such as quercetin, which suppress NF-κB [279]. A study on adipocytes showed that quercetin enhanced the gene expression of irisin, an adipokine that has a direct association with exercise and is inversely related to the TG content of hepatocytes [280]. In a RCT of 87 overweight NAFLD patients, supplementation with 3000 mg/day of cardamom extract for 3 months significantly lowered fasting plasma glucose, insulin, and TG ($p<0.05$ for all), in addition to improving the grade of steatosis and serum irisin levels ($p<0.05$) when compared to baseline [281]. Moreover, cardamom supplementation may improve several biomarkers related to fatty liver, including inflammation, ALT, and sirtuin1 in overweight/obese NAFLD patients [282,283]. Further pharmacodynamic studies and long-term RCTs are needed to confirm these preliminary results.

Another plant potentially useful in NAFLD is Phyllanthus urinaria which was reported to reduce both hepatic steatosis and necroinflammation *in vitro* and *in vivo* studies [284]. However, the bioactive molecules responsible for this anti-NAFLD effect have not been fully identified. In a RCT which enrolled 60 patients with NASH (confirmed histologically), supplementation of 3 g/day of Phyllanthus for 24 weeks was not found to be superior to placebo in improving NAFLD activity score in these patients as assessed by biopsy [285].

L-Carnitine is essential for a number of intracellular and metabolic functions and thus could exert positive effects in NAFLD. In a RCT which included 74 patients with NASH, L-carnitine supplementation (2 g/day for 24 weeks) was shown to improve both insulin and inflammatory biomarkers such as AST ($p=0.000$), ALT ($p=0.000$), γ-GT ($p=0.000$), glucose ($p=0.000$), HOMA-IR ($p=0.000$), hs-CRP ($p=0.000$), TNF-α ($p=0.000$), and histological scores ($P=0.000$) [286]. However, another RCT of 80 NAFLD patients treated with 500 mg/day of L-carnitine for 1 year showed no significant changes in liver function tests or ultrasound findings [287].

Vitamin C (ascorbic acid) is a powerful antioxidant, capable of scavenging free radicals [288]. Vitamin C supplementation has been shown to enhance SOD and GPxactivity, reducing oxidative stress and inflammation (expressed as CRP and myeloperoxidase levels) [289]. Vitamin C treatment may be also inversely associated with the grade of liver steatosis and inflammation, acting via regulation of adiponectin levels and inhibition of hepatic steatosis via an increase in the mRNA levels of PPARα-dependent fatty acid β-oxidation genes [290]. Vitamin C may also improve glucose metabolism and insulin sensitivity, as well as playing a role in circulating and hepatic lipid homeostasis [291]. In this regard, in children with NAFLD, a decrease in serum vitamin C levels was correlated with increased hepatic ballooning [292]. Han *et al.* showed a positive association between low vitamin C intake and NAFLD in Korean subjects [293]. Similar results were obtained by Wei et al. in middle-age and older people [294]. However, a study by Madan *et al.* reported no difference in plasma vitamin C levels between NAFLD patients and a healthy control population [295]. As described above, most interventional studies have been conducted using a combination of vitamin C and E, with or without conventional therapies. In this context, Harrison et al. reported an improvement of hepatic fibrosis in NASH patients after vitamin C and E supplementation [296]. Foster et al. also observed a reduction in hepatic steatosis by 71% in individuals with NAFLD after vitamin C, E, and atorvastatin (20 mg) administration [297]. Nevertheless, other studies suggested that vitamin C did not provide additional benefit over lifestyle interventions [298]. For these reasons, the role of vitamin C in NAFLD remains controversial and there is a need for further investigation.

Betaine is a dietary supplement, which can also be synthesized *in vivo* from choline. It is well-known to act as a methyl donor for the conversion of homocysteine to methionine and thus, to be potentially useful in people with hyperhomocysteinemia [299]. In recent years, betaine has been studied in the treatment of AFLD with satisfactory results [300,301]. In animal models of NAFLD, betaine administration was shown to improve glucose metabolism and adipocyte insulin signalling. The hepatoprotective effects of this supplement probably relate to the reduction of oxidative stress, activation of the AMPK, fibroblast growth factor 10 (FGF10) and adipose triglyceride lipase (ATGL) protein levels, and restoration of the phosphatidylcholine generation [302]. In NASH patients, betaine has been reported to decrease indexes of steatosis [303].

Supplementation for 12 weeks, with 30 g/day of **brown milled flaxseed**, in 50 individuals with NAFLD, was associated with an improvement in BMI, waist circumference, serum transaminases, hs-CRP, TNF-α, glucose and insulin concentrations when compared with placebo. In addition, even though HOMA-IR, hepatic fibrosis, and steatosis scores (confirmed by fibroscan examination) were improved in both groups, the improvement was significantly greater in the flaxseed group [304].

Pre-clinical data for Chlorella vulgaris, Myrica (**bayberry**) and **garlic** are also interesting, suggesting a possible role as anti-inflammatory, antioxidant, and anti-steatosis agents. Nevertheless, studies on individuals with liver steatosis are lacking and the follow up has generally been short [305].

Finally, a nutraceutical approach may come from traditional Chinese medicine. In fact, the administration of combined Artemisia capillaris (Thunb), Gardenia jasminoides (Ellis), and Rheum palmatum (L) has been found to decrease hepatic fat accumulation, promote endothelial progenitor cell proliferation, enhance adiponectin secretion, and increase the expression of PPAR-γ [306]. Table 4

4. Discussion

In the present dearth of specific pharmacological therapies indicated for the management of NAFLD, the use of certain nutraceuticals is an attractive proposition (Fig. 2). In combination with diet and lifestyle-based interventions to promote weight loss and reduce insulin resistance, nutraceuticals may have an important role in NAFLD therapy.

Since a growing body of evidence indicate that NAFLD develops because of a complex interaction between genetic susceptibility and other environmental factors, the interface between the nutritional environment and cellular/genetic processes ("nutrigenomics") cannot be underestimated. As elsewhere reviewed, since an individual's genetic makeup influences how nutrients/nutraceuticals are assimilated, stored, and excreted, personalized nutrition and prescription of supplements which takes into account the genetic features of patients could have immediate potential for clinical translation, representing an individualized therapeutic approach to the disease [307].

Data concerning silymarin, vitamin E, polyunsaturated fatty acids of the ω-3 series, coenzyme Q10, berberine and curcumin are particularly encouraging. These nutraceuticals exert hepatoprotective activity and beneficial actions on CV system. Results from clinical trials evaluating the use of vitamin D are conflicting.

However, challenges remain in terms of implementing nutraceutical interventions in the presence of NAFLD in an Evidence-Based approach to therapy. This may be attributed in part to the relative limitations of trials in this area compared with Phase 3 studies of novel pharmaceuticals. With respect to herbal extract, the clinical literature frequently does not report details about the standardization of extracts, and the presence of contaminants that may confound the findings of some studies. Furthermore, clinical studies of nutraceuticals often have relatively small sample sizes and a short duration of follow-up, thus base their conclusions on surrogate endpoints, rather than patient-orientated clinical outcomes [308]. Also, compared with conventional pharmaceuticals, the beneficial changes in biomarkers elicited by nutraceuticals in various conditions are frequently modest. Therefore, very large trial populations may be necessary to demonstrate the effect of a particular nutraceutical on a particular disease-related outcome.

Table 4
Recommendations for the supplementation of nutraceuticals in patients with NAFLD.

Nutraceutical	Raccomandation	Active daily doses	Effects on lab parameters	Liver ultrasound scan
Omega-3 fatty acids (EPA and DHA)	+++**O**	2-4 g EPA and DHA	↑ insulin sensitivity and HDL-C; ↓ AST, ALT, GGT, lipid peroxidation, TG, LAP, HIS, hs-CRP, IL-6, MCP-1, ICAM-1, VCAM-1, MMP-9, BMI and blood pressure (SBP 1-5 mmHg)	↓ degree of steatosis
Silymarin	+++**O**	100-500 mg	↓ lipid peroxidation, AST, ALT, GGT, FPG, LAP, HIS and basal insulinemia	↓ degree of steatosis assessed by liver ultrasound scan or liver biopsy
Berberine	+++**O**	500-1500 mg	↑ insulin sensitivity, HDL-C; ↓ lipid peroxidation, LDL-C, TC, TG, FPG, LAP, HIS, hs-CRP, IL-6, MCP-1, ICAM-1, VCAM-1, MMP-9, HOMA index	↓ degree of steatosis
Coenzyme 10	++OO	100-300 mg/day	↓ lipid peroxidation, AST, ALT, GGT, hs-CRP, ↑ adiponectin/leptin ratio	↓ degree of steatosis
Curcumin	++OO	100-1500 mg	↑ insulin sensitivity; ↓ lipid peroxidation, AST, ALT, TC, LDL-C, MCP-1, ICAM-1, VCAM-1, IL-6, TNF-α, MMP-9 and HOMA index	↓ degree of steatosis
Artichoke leaf extract	++OO	1000-2000 mg	↑ insulin sensitivity, ↓ lipid peroxidation, AST, ALT, TG, TC and LDL-C	Not investigated
Green tea (catechins)	++OO	250-1200 mg of green tea extract or 170-850 mg of EGCG	↑ insulin sensitivity; ↓ lipid peroxidation, AST, ALT, ALP, TC and LDL-C	Not investigated
Probiotics	+OOO	1-100 billion	↑ insulin sensitivity; ↓ lipid peroxidation, low-grade inflammation (TNF-α, hsCRP), AST, ALT, HIS, LAP, GGT and LDL-C	↓ degree of steatosis (also confirmed biopsy)
Prebiotics	+OOO	oligofructose, psyllium and inulin	↓ levels of transaminases, TG and LDL-C, glucose metabolism and insulin resistance; ↑ GLP-1 levels	Not investigated
Resveratrol	+OOO	100-300 mg	↑ insulin sensitivity; ↓ lipid peroxidation and low-grade inflammation (TNF-α, hsCRP)	Not investigated
Vitamin D	+OOO	1000-5000 UI	↓ resistin, IL-4, IL-6 and expression of inflammatory genes such as TNF-α and TGF-P, modulation of TLR2, TLR4 and TLR9	Not investigated
Vitamin E	+OOO	100-1200 UI	↓ malondialdehyde, TNF-α IL-1, IL-2, IL-4, IL-6, and IL-8, serum ALT and AST activity	↓ degree of steatosis (also confirmed by liver biopsy)
Astaxanthin	+OOO	5-20 mg	↑ insulin sensitivity, SOD, CAT, GPx activity, GSH; ↓ lipid peroxidation, IL-6, TNF- α, liver CD4 and CD8 recruitment	Not investigated

ALT = alanine aminotransferase, ALP = alkaline phosphatase, AST = aspartate aminotransferase, BMI = body mass index, CAT = catalase, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, FPG = fasting plasma glucose, GGT = gamma-glutamyl transferase, GLP-1 = glucagon-like peptide 1, GPx = glutathione peroxidase, hs-CRP = high sensitivity C-reactive protein, HIS = hepatic steatosis index, ICAM = intercellular adhesion molecule, IL = interleukin, LAP = lipid accumulation product, LDL-C = low density lipoprotein cholesterol, MCP-1 = monocyte chemoattractant protein-1, MMP = matrix metalloproteinases, SBP = systolic blood pressure, SOD = superoxide dismutase, TC = total cholesterol, TG = triglycerides, TLR = Toll-like receptors, TNF-α = tumor necrosis factor-α, VCAM = vascular cell adhesion protein, WC = waist circumference

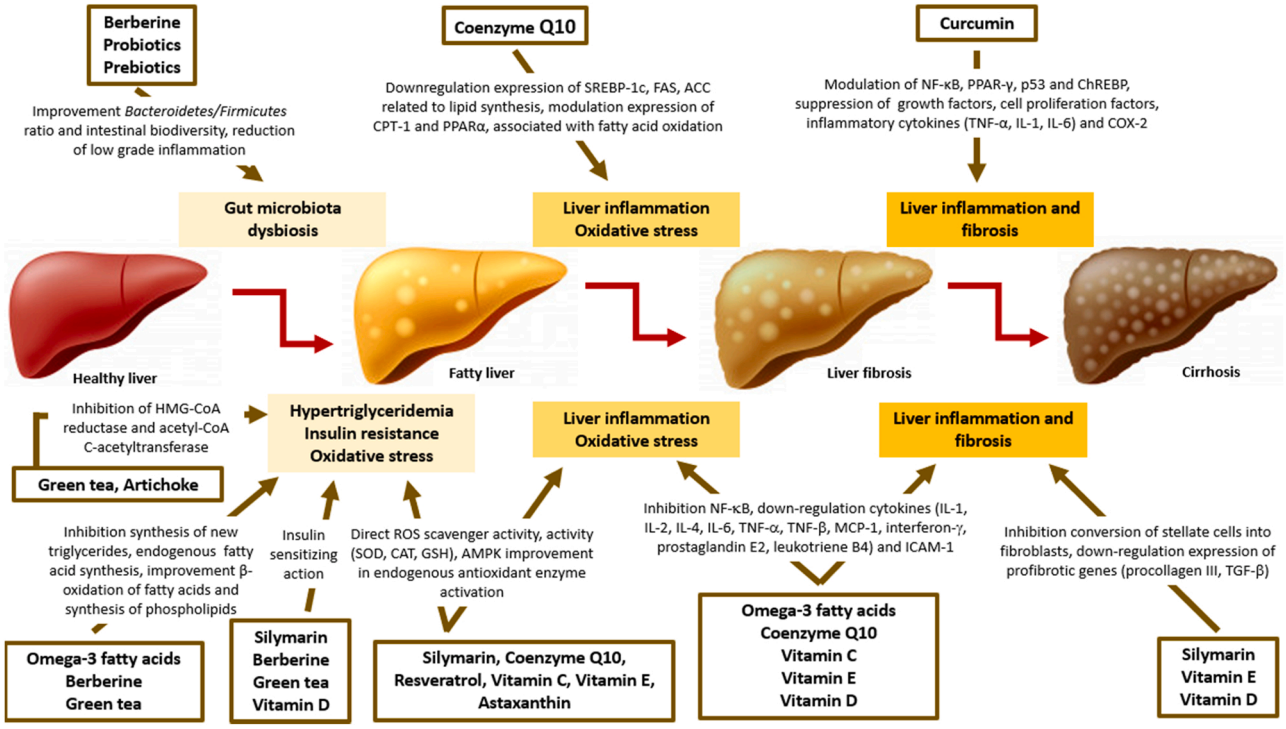

Fig. 2. Nutraceutical actions on the four stages of NAFLD.

Nevertheless, nutraceuticals may still have important effects on health, when small changes in exposure to harmful stimuli (such as inflammation, LDL-C, hypertension) can be sustained over a long period of time [309]. Many nutraceuticals have complementary actions, and when used in combination, can have greater effects on a range of biological targets [310–315]. NAFLD has overlapping risk factors with CVD and a range of other conditions. Therefore, a nutraceutical combination therapy ostensibly prescribed for NAFLD may well have benefits in a range of diseases, which may go unreported, if a trial is specifically focused on a single endpoint.

Whereas many clinical trials of nutraceuticals focus on the evaluation of a particular ingredient, on a specific outcome, consideration should be given to the potential to conduct large trials, recruiting diverse populations, and treating them with high-quality 'polypill' combination nutraceutical formulations (manufactured in accordance with the principles of Good Manufacturing Practice), and measuring the effect of these interventions on clinically relevant outcomes over a period of years. The formulation of such polypills could be devised based upon nutraceuticals with well-defined mechanism of action (in preclinical studies), demonstrated safety in clinical use, and efficacy against biological targets with relevance in a range of disease states. Such large trials would allow for meaningful and rigorous subgroup analyses, such that the effect of a nutraceutical polypill could be evaluated as part of a larger trial recruiting patients with a wide range of metabolic diseases. Such a wide-ranging trial may be more likely to attract funding and participation than a narrowly focused study.

In addition, an active nutrivigilance service (both national and international) should be ensured to monitor the long-term safety of these substances. Indeed, given the scarcity of long-term studies (> 6 months), the constant monitoring of the effects of nutraceuticals must be proposed and considered. The quality of a nutraceutical is the "*conditio sine qua non*" for both the effectiveness and final safety. However, quality must necessarily be defined by objective values that rely on validated criteria and not on subjective and imaginative considerations. In other words, a quality nutraceutical cannot be defined if the raw materials (with the maximum permitted levels of toxic substances), the formulation strategies and the production processes are not clearly known.

Of course, many other nutraceuticals may exert positive effects on NAFLD, and further investigation of such agents is warranted, firstly in preclinical studies, then in clinical trials. Finally, as mentioned above, several traditional Chinese herbal formulas have been reported in the literature to exert significant anti-NAFLD effects, including the combination of *Artemisia capillaris* (Thunb), *Gardenia jasminoides* (Ellis), and *Rheum palmatum* (L).

In conclusion, a relatively large number of dietary supplements and herbal extracts seems to improve NAFLD-related biochemical and histological features and may be useful as an adjunctive supplementation therapy but cannot replace pharmacotherapy. However, an evidence-based approach is needed. In particular, long-term, well-designed RCTs are still needed to elucidate if the observed results are confirmed and maintained over time. Furthermore, the molecular targets and the signaling transduction pathways of many of these nutraceuticals should be extensively investigated. With respect to plant extracts, the eventual additive or synergistic effect of each single bioactive compounds must be clarified. However, despite these gaps in our knowledge, an increasing body of clinical evidence highlights the potential for specific nutraceutical agents to be used in the management of NAFLD.

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No experimental or clinical work was conducted, no patient data was used, therefore no ethical approval was required for this work

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M.R., A.C., A.F.G.C: Conceptualization; Data curation; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing – original draft; **P.E.P., N.K., D.P.M., P.P.T., I.G-B, J.M., D.M., P.M., M.R., A.S., D.V.**: Writing – review & editing, Revisions, M.B.: Conceptualization; Methodology; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing, Revisions, Journals submission.

Declaration of Competing Interest

Manfredi Rizzo: speakers bureau: Amgen, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Meda, Mylan, Merck Sharp & Dohme, Novo Nordisk, Roche Diagnostics, Sanofi, and Servier; consultant to Amgen, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Meda, Mylan, Merck Sharp & Dohme, Novo Nordisk, Roche Diagnostics, Sanofi, and Servier; Medical and Scientific Advisor, Europe East and South at Novo Nordisk; *Peter E. Penson* has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Mylan, Napp, Sanofi; *Niki Katsiki*; *Dimitri P. Mikhailidis* has given talks, acted as a consultant or attended conferences sponsored by Amgen and Novo Nordisk; *Peter P. Toth:* speakers bureau: Amgen, Esperion, Kowa, Merck, Novo-Nordisk; consultant to Amarin, bio89, Kowa, Merck, Resverlogix, Theravance; *Maciej Banach:* speakers bureau: Amgen, Herbapol, Kogen, KRKA, Polpharma, Mylan/Viatris, Novartis, Novo-Nordisk, Sanofi-Aventis, Teva, Zentiva; consultant to Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, Novartis, Novo-Nordisk, Polfarmex, Sanofi-Aventis; Grants from Amgen, Mylan/Viatris, Sanofi and Valeant; CMO at Nomi Biotech Corporation Ltd.; all other authors have no conflict of interest.

Data Availability

No data was used for the research described in the article.

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