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Review

Medicinal plants and bioactive natural compounds in the treatment of non-alcoholic fatty liver disease: A clinical review

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a major cause of liver diseases, and is closely related to metabolic syndrome and its related conditions, diabetes mellitus and dyslipidemia. On the other hand, NAFLD as a multisystem disease increases the risk of several chronic diseases include type 2 diabetes mellitus, cardiovascular disease (CVD), and chronic kidney disease. The main objective was to review the efficacy of bioactive natural compounds assessed by clinical trials. Search literature using four databases (PubMed, EBSCO, Web of Science, and Ovid Medline) to review publications that focused on the impact of bioactive natural compounds in NAFLD treatment. Due to the lack of effective pharmacological treatments available for NAFLD, lifestyle modifications such as following a healthy diet, vigorous physical activity, and weight reduction remain the first line of treatment for NAFLD. However, due to the poor adherence to this type of treatment, especially for long-term weight loss diets some of which may have harmful effects on the liver, finding novel therapeutic agents for NAFLD treatment and/or preventing NAFLD progression has garnered significant interest. Although the therapeutic agents of NAFLD treatment have been reviewed previously, to date, no summary has been conducted of clinical trials examining the effects of herbal compounds on NAFLD-related biomarkers. This review highlights the beneficial role of herbal bioactives and medicinal plants in NAFLD treatment, particularly as complementary to a healthy lifestyle. All natural products described in this review seem to have some benefits to improve oxidative stress, cellular inflammation and insulin-resistance, which always remain as the "primum movens" of NAFLD pathogenesis.

Contents

Abbreviations: ApoA-I, apolipoprotein A1; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHE, cholinesterase; CT, computerized tomography; CVD, cardiovascular diseases; FLI, fatty liver index; FFA, free fatty acid; GGT, gamma-glutamyl transpeptidase; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HFC, hepatic fat content; HOMA-IR, homeostasis model of assessment-insulin resistance; HOMA-β, homeostasis model of assessment-estimated β cell function; hs-CRP, high-sensitivity C-reactive protein; HSI, hepatic steatosis index; IL-6, interleukin 6; LAP, liver accumulation product; LDL-C, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; NAFLD-FS, NAFLD-Fibrosis score; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor κB; QUICKI, quantitative insulin sensitivity check index; TG, triglycerides; TNF-α, tumor necrosis factor alpha; WC, waist circumference.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a major cause of liver diseases, which is defined as an excessive fat accumulation, particularly triglycerides, in the liver [1,2]. The main causative factor of excessive liver fat is obesity, especially central obesity, which is strongly correlated with insulin resistance [1]. Indeed, NAFLD is closely related to metabolic syndrome and its associated features, diabetes mellitus and dyslipidemia. Paralleling increases in these chronic diseases, NAFLD has become the most prevalent liver disease among both adults and children, with a prevalence that has doubled over the last 20 years [1–4]. Progression of NAFLD results in the development of nonalcoholic steatohepatitis (NASH), which is a strong predictor of cirrhosis, liver failure, and hepatocellular carcinoma [2,5]. Notably, NAFLD is expected to be the most frequent reason for liver transplantation by 2030 [5]. However, cardiovascular disease (CVD) is considered the main cause of death among NAFLD patients [5]. It has been shown that NAFLD, as a multisystem disease, could affect extra-hepatic organs and regulatory pathways, which increases the risk of several chronic diseases, including type 2 diabetes mellitus, CVD, cardiac diseases, and chronic kidney disease [1,5].

NAFLD is a multifactorial disease with a complex pathogenesis [6,7]. The pathogenesis of NAFLD was initially explained based on the "2-hit hypothesis" which suggested that hepatic TG accumulation or steatosis is the first hit and the second hit is triggered by inflammatory cytokines/adipokines, mitochondrial dysfunction and oxidative stress leading to steatohepatitis and/or hepatic fibrosis [8]. Today, it has been shown that free FFAs directly promote liver injury. Several risk factors and mechanisms are considered by which excessive triglycerides are accumulated in hepatocytes causing NAFLD including excess body fat (overweight and obesity), insulin resistance, inflammation, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, bacterial overgrowth and genetic predisposition [6–9]. It has been shown that excess body fat, in particular central obesity and visceral fat, is closely associated with NAFLD [9]. Similarly, several studies have suggested that insulin resistance, the key pathophysiological factor of metabolic syndrome, is independently and strongly related to NAFLD [9]. Insulin suppresses adipose tissue lipolysis thus in insulin resistance situation, increased efflux of FFAs from adipose tissue occurs. In addition, insulin resistance accompanies impairment of glycogenesis, increased gluconeogenesis and glycogenolysis. Oxidative stress, an imbalance between the production of ROS and protective antioxidants, is another important factor in NAFLD pathogenesis that is associated with inflammation and lipotoxicity of FFAs [6,10] (Fig. 1). Western diet, which is rich in saturated fatty acids and fructose is another independent factor strongly linked to NAFLD. Liver has a little capacity for storage of lipids; at first, energy received from glucose, fructose and lipids is stored as glycogen, and the excess energy received from fat is redistributed to peripheral tissues for storage in adipocytes or use for energy production [6,11]. In NAFLD, increased intrahepatocellular lipids occurs due to dysregulated processes of lipid trafficking [12]. This can lead to organelle failure, including mitochondrial dysfunction and endoplasmic reticulum stress, ROS generation and insulin resistance [6,13,14]. When lipids are overloaded in the white adipose tissue, the place for TG storage, metabolic incompetence and subsequent macrophage infiltration occurs [6,15,16]. A large body of evidence has shown that macrophage infiltration could cause low-grade inflammation by increasing the production of inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [15,16]. Finally, although it has been shown that environmental factors such as obesity, insulin resistance and unhealthy dietary patterns are the major factors contributing to NAFLD and NASH, genetic predisposition should be considered as another risk factor [8]. Gene polymorphisms linked to lipid metabolism, insulin resistance, oxidative stress, cytokines/adipokines and fibrogenesis could all increase vulnerability to NAFLD and NASH [8]. The current concepts of the complex mechanisms involved in NAFLD pathogenesis are illustrated in Fig. 1.

To date, no ideal pharmacological treatment has been made available for NAFLD [17]. Therefore, lifestyle modification, which includes following a healthy diet and vigorous physical activity along with weight reduction, remains the first line treatment for NAFLD [17–19]. However, due to the poor adherence to this type of treatment, especially for long-term weight loss diets, some of which may have harmful effects on the liver [17,18,20], there is significant interest in identifying therapeutic agents for the treatment and/or prevention of NAFLD progression. Due to potential adverse

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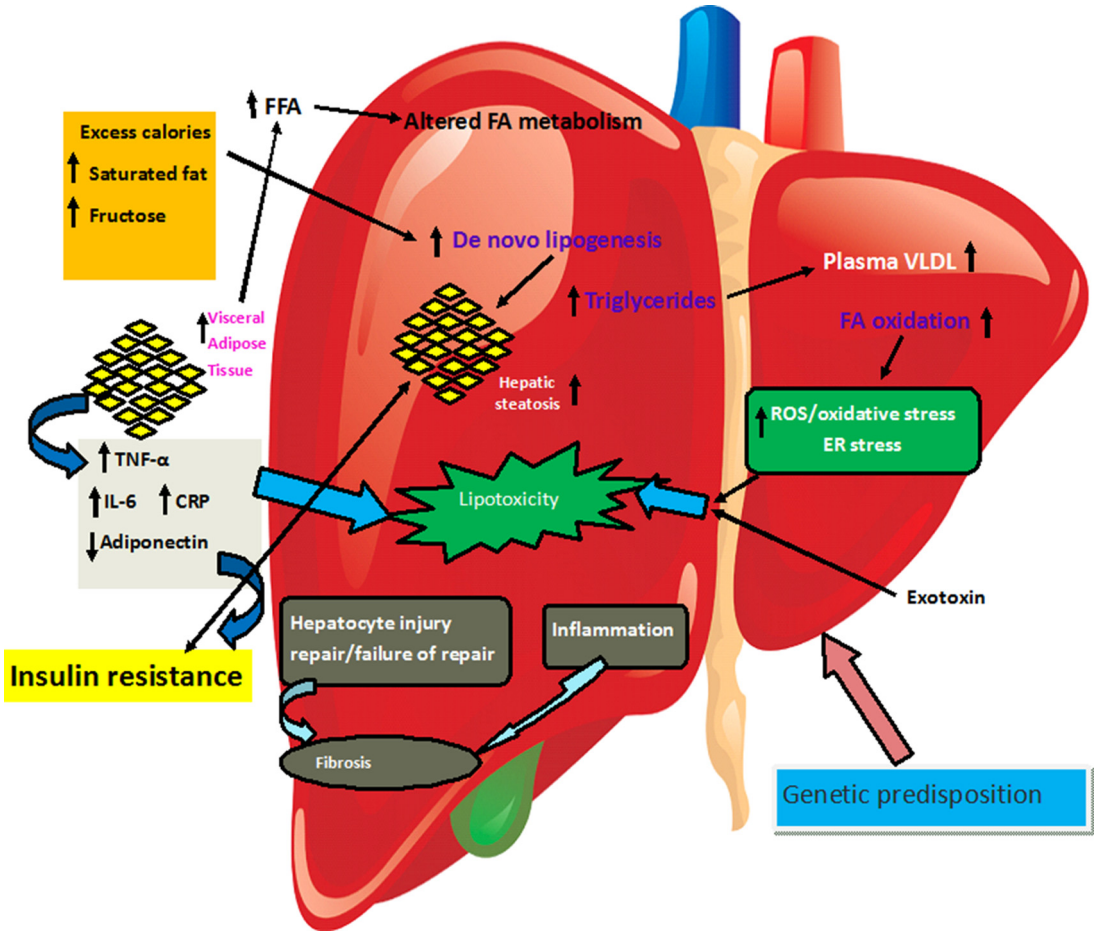

Fig. 1. Pathophysiological mechanisms of NAFLD. Increased caloric intake in combination with increased saturated fat and fructose consumption, leads to increased visceral adipose tissue (VAT); fructose consumption also stimulates de novo lipogenesis (DNL) and does not cause the satiety signaling that occurs with glucose. VAT is a metabolically active tissue that produces numerous proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), and is associated with decreased adiponectin, an adipokine with anti-inflammatory activities. Both VAT and hepatic steatosis are inter-related to insulin resistance and hyperinsulinemia and in a feed-forward manner. VAT also increases delivery of free fatty acids (FFAs) to the liver *via* the portal circulation, resulting in an increased load of FA metabolism within the liver, DNL, increased reesterification of triglycerides, and increased oxidation. In some patients, compensatory mechanisms to prevent lipotoxicity from the altered FA metabolism fail, resulting in steatohepatitis and fibrosis. The circulating proinflammatory cytokines from VAT, increased reactive oxygen species (ROS) from oxidative stress and endoplasmic reticulum (ER) stress, and increased portal endotoxins have all been speculated to play a role in lipotoxity. Failure of hepatocyte repair and inflammation perpetuates the process(es) that initiate and promote fibrosis [6]. Abbreviation: VLDL: very low density lipoprotein.

effects of conventional medical therapies, there has been a focus on studying complementary therapies that are both natural and safe products, such as herbal medicine and functional foods (e.g., fruits, vegetables) as dry materials or their extracts [21,22]. Although the therapeutic agents of NAFLD treatment have been reviewed previously, to date, no summary has been conducted of human clinical trials examining the effects of herbal compounds on NAFLD-related biomarkers. Thus, the main objective was to review the efficacy of bioactive natural compounds assessed by clinical trials.

2. Subjects and methods

The reporting of this narrative review has been done in accordance with the PRISMA guidelines.Medline, Web of Science, SCOPUS and Google Scholar databases were using the following search terms in titles abstracts: medicinal plants OR herbal bioactive OR bioactive natural compounds OR nutraceutical in NAFLD; AND random OR randomized OR randomly OR randomization OR "randomized controlled trial" OR "randomized trial" OR "randomized study" OR "random number" OR placebo. Were excluded the studies that not treated the NAFLD or NASH and these of 10 years old. The search was limited to studies in English language. The literature was searched from inception to January 01, 2017.

Two researchers (VN and CNB) independently systematically screened the major bibliographic databases. Reference lists from all selected articles we also examined for additional relevant studies.

3. Herbal bioactive compounds in the treatment of NAFLD

3.1. Flaxseed

Flaxseed is an important functional food, which contains high amounts of ω-3 α-linolenic acid, dietary soluble and insoluble fibers, and being a rich source of lignans, known for its antioxidant and estrogen-like properties [23]. It has been shown that flaxseed has several health benefits including the potential to reduce risk for CVD, atherosclerosis, diabetes, metabolic syndrome and dyslipidemia, cancer, arthritis, osteoporosis, autoimmune and neurological disorders [23–27]. The role of flaxseed in NAFLD was recently assessed in a randomized controlled trial [28]. In this study, a total of 50 NAFLD cases confirmed by fibroscan examination were recruited and randomized to undergo lifestyle modification (control) or lifestyle modification with 30 g/day of brown milled flaxseed supplementation for 12 weeks. At the end of the study, significant reductions were found in BMI, WC, serum ALT, AST, GGT, hs-CRP, TNF-α, glucose and insulin concentrations, along with

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HOMA-IR, and hepatic fibrosis and steatosis scores in both groups; however, these improvements were significantly greater in the flaxseed group compared to control. In addition, serum total cholesterol and LDL-C were significantly decreased in both groups, while there were no significant differences between the study groups. No serious side effects were reported by the study participants [28].

3.2. Cinnamon

Cinnamon is spice derived from the inner bark of several tree species from the genus *Cinnamomum*, which has been used for thousands of years as a food flavoring with potential health effects [29]. Due to cinnamon having several potential health benefits such as antioxidant and insulin-sensitizing properties, this natural botanical product has recently become the subject of numerous studies conducted by many scientists around the world [30,31]. It is hypothesized that cinnamon could stimulate insulin release, increase insulin sensitivity, enhance insulin disposal, and exert activity in the regulation of protein-tyrosine phosphatase 1B (PTP1B) and insulin receptor kinase, indicating the potential insulinotropic effects of this spice [31,32]. As several randomized clinical trials, systematic reviews and meta-analyses have confirmed the therapeutic role of cinnamon in lowering blood glucose and improving lipid profile [30,31,33,34], it is postulated that cinnamon might be useful in the treatment of NAFLD. To investigate this hypothesis a randomized clinical trial was recently conducted, in which 50 NAFLD patients diagnosed by ultrasonography were assigned into two groups to receive either two capsules of cinnamon each day (750 mg cinnamon per capsule), or receive two placebo capsules (wheat flour) daily [35]. After 12 weeks of the intervention, fasting blood glucose, HOMA-IR, QUICKI, serum total cholesterol, triglycerides, ALT, AST, GGT, and hs-CRP were decreased significantly in the cinnamon group in comparison to the placebo group. Serum LDL-C was decreased significantly in both groups, while no changes were observed in BMI, WC, and HDL-C in either study groups [35].

3.3. Green tea

Green tea is one the most well-known beverages to contain high amounts of flavonoids with antioxidant properties. The major flavonoids in green tea are the catechins which constitute about 20% of green tea flavonoids [36]. Green tea and catechins have been the subject of significant interest after research has demonstrated anti-tumor [36], anti-cancer [37], anti-hypertensive [38], anti-arteriosclerotic [36], antioxidant [39], anti-thrombotic [40], anti-hyperglycemic [41,42] and hypolipidemic properties [43,44]. It has been proposed that green tea as a high source of catechins may improve liver function and fatty liver status in NAFLD patients, hence, the impact of green tea on NAFLD patients has recently been assessed. In a double-blind, placebo-controlled study, 17 adults with NAFLD were randomly allocated to three groups: the first group consumed 700 mL of green tea with high-density catechins (contained 1080 mg catechins), the second group consumed 700 mL of green tea with low-density catechins (contained 200 mg catechins), and the placebo group consumed 700 mL of a green tea-flavored beverage (contained 0 mg catechins) for 12 weeks [36]. To determine the size of each patient's liver and spleen, ultrasonography and computed tomography (CT) were performed. At the end of study, although the largest reductions in body weight and BMI were seen in the high-density catechins group, these were not significant when compared to the other groups. However, the reduction in body fat percentage was significantly greater among high-density catechins patients than other groups. In addition, a greater improvement was found in the liver-to-spleen CT attenuation ratio among high-density catechins group compared with the other groups. Serum ALT and urine 8-isoprostane (a specific marker of oxidative stress) were reduced in all three groups, however, the reduction in the high-density catechins group was significantly greater than the other groups [36].

In another double-blind, placebo-controlled, randomized clinical trial study, the effect of green tea extract in NAFLD patients was investigated [45]. Ultrasonography was used to diagnose fatty liver. A total 80 obese adult patients with elevated serum ALT and AST and without other hepatic diseases were assigned for 12 weeks to either an intervention group who received a green tea extract (GTE) supplement (500 mg GTE tablet per day) or a control group given placebo tablets containing pure microcrystalline cellulose. At the end of study, BMI was significantly reduced in both groups, though its reduction was significantly greater in the green tea group compared with placebo. Serum ALT and AST significantly decreased in the green tea group, although these changes were not significantly different compared to the control group. Serum alkaline phosphatase (ALP) also significantly decreased in both groups, however, its reduction was significantly greater in the green tea group [45].

3.4. Silymarin/Silybin

One of the most popular plants in the treatment of liver disease is *Silybum marianum*, or milk thistle [46]. A common extract of milk thistle is silymarin, which has several flavonolignans and a flavonoid [47]. Silybin is the most prevalent and important component of silymarin, which has shown biological effects [47]. Due to their potential antioxidant, anti-inflammatory and anti-fibrotic properties, silymarin/silybin are used as therapeutic agents to treat different types of liver diseases [46,47]. The protective role of silymarin/silybin in preventing NAFLD progression could be explained by attenuating oxidative stress, insulin resistance, liver fat accumulation and mitochondrial dysfunction. Moreover, silybin could play a substantial role in the treatment of NAFLD, through inhibition in intrahepatic glycolysis and gluconeogenesis and modulation of inflammation, apoptosis and fibrogenesis [46,47]. However, the major limitations of using silymarin/silybin are their low water solubility, resulting in poor intestinal absorption and low bioavailability. To solve this problem, a complex of silybin with phosphatidylcholine has been used to improve water solubility [47]. In addition to animal studies [46], some human studies have evaluated the efficacy of silymarin/silybin for the treatment of NAFLD. In a recent clinical trial, 30 overweight patients with NAFLD were randomized into three groups, to receive a personalized Mediterranean diet in group A and B, or receive no treatment in group C (control). In group B, subjects were also given 2 pills daily of Realsil complex (a complex of 94 mg silybin with 194 mg phosphatidylcholine, co-formulated with 30 mg α-tocopheral) [48]. Liver ultrasound was used to diagnose NAFLD. After 6 months intervention, in both group A and B weight, BMI, waist and hip circumferences, serum TG, total cholesterol and fatty liver index were reduced significantly in comparison to the control group. In addition, in the group taking the Realsil complex, significant improvements were observed in insulin sensitivity, fasting glucose, insulin and HOMA-IR compared with the control group. Moreover, compared to baseline, at the end of study Hamaguchi score (scoring of hepatic fat accumulation) was significantly reduced in both intervention groups. None of the study participants reported any adverse effects [48].

In another double-blind clinical trial, the efficacy of silybin was assessed in 179 adults with NAFLD [49]. In this study, patients were randomized to either intervention groups who received 2 pills of Realsil daily or placebo. Histologically documented liver steatosis or steatohepatitis diagnosed within 12 months and elevations in ≥1 marker of liver damage(AST, ALT, or GGT) within 6

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months were the inclusion criteria for the study. After 12 months of intervention, the proportion of patients with normalized AST, AST and GGT levels significantly increased in those taking Realsil, but not in the placebo group. However, no significant change was found between the two groups in the degree of liver steatosis, which was assessed by ultrasonography at the end of the study. Furthermore, BMI, waist–hip ratio and abdominal circumference did not significantly change in any groups. Although, blood glucose was 31% lower compared to baseline at the end of the study in the intervention group, the differences between groups were not significant. Moreover, the intervention had no notable effects on plasma cholesterol, plasma TG, and quality of life. Transient adverse effects were in study subjects, and included diarrhea, dysgeusia, and pruritus; however, these side effects were not serious [49].

In a clinical trial, Federico et al. [39] evaluated the effectiveness of silybin in 85 outpatients; 59 were affected by early-stage NAFLD (group A) and 26 by hepatitis C virus (HCV)-related chronic hepatitis in combination with NAFLD (group B). All patients were histologically diagnosed with liver disease for ≤two years prior to the study. In this study, subjects were randomly assigned to either receive no treatment (20 NAFLD; 12 HCV) or receive 4 pills daily of Realsil for 6 months, followed by another 6 months of follow up (39 NAFLD; 14 HCV). At the end of study, ultrasonography showed that steatosis, graded from 0 to 3, was significantly improved in the NAFLD group (group A) undergoing treatment. The level of liver enzymes decreased only in treated patients after 6 months, although this was maintained after 12 months only in those without HCV (group A). In addition, significant reductions in serum insulin were observed only in treated patients. Indices of liver fibrosis (plasma transforming growth factor β, hyaluronic acid, and metalloproteinase 2) were measured and were significantly reduced in both treated groups, however, these changes were maintained at 12 months only in those with HCV (group B). The intervention had no adverse events [50].

In one randomized clinical pilot study, 36 NAFLD patients (confirmed by percutaneous liver biopsy) were recruited to two groups: the first group was given 2 tablets of EuroSil 85(540.3 mg *Silybum marianum Gaerth*, plus 36 mg vitamin E) per day and followed a lifestyle modification program comprised of a hypocaloric diet (1520 kcal, 52% kcal as carbohydrates, 25% kcal as fat and 23% kcal as protein) and exercise for 3 months; a second group only followed the lifestyle modification program for 3 months [51]. At the end of the 3 month intervention, both groups had reductions from baseline in body weight, BMI, WC, serum GGT, as well as fatty liver index and NAFLD-fibrosis score. However, blood glucose, HOMA-IR and serum ALT were significantly decreased only in the second group, whereas serum TG and AST did not significantly change in any of the groups. No adverse effects were reported by the study subjects [51].

A randomized controlled trial was conducted in 78 participants with metabolic syndrome whom had liver steatosis confirmed by ultrasound. All patients followed a standard regimen of diet and exercise for 90 days. Additionally, approximately half of the patients (group A) were treated with 2 pills/day of Eurosil 85 (silymarin with vitamin E), whereas no additional treatment was given to the remaining participants (group B) [52]. After three months of the intervention, BMI, abdominal circumference, ultrasound measurement of right liver lobe (cm), hepatic steatosis index (HSI), and liver accumulation product (LAP) were decreased in both groups; however, changes in group A were significantly greater than changes in group B (control group). Hemogolbin A1c (HbA1c) actually increased in both groups, though the increase was significantly larger in the control group. No significant differences between the groups were observed in any of the other parameters measured, including fasting plasma glucose, ALT, AST, GGT, TG, LDL-C and HDL-C. None of the study participants reported any side effects [52].

3.5. Soy

Soybeans have many bioactive components, which could potentially be beneficial for human health in the prevention and treatment of chronic diseases, such as CVD, diabetes and NAFLD [53]. Isoflavones, with both hormonal and non-hormonal activities, are considered the major bioactive constituents of soybean. Other components of soy include saponins, soy protein or peptides, phospholipids and flavonoids. These additional components may have hormonal, immunological, and bacteriological activities and affect digestive health [53]. Several animal studies have shown that components of soy improve NASH and NAFLD through different mechanisms, including improving insulin resistance, decreasing hepatic lipid deposition, and increasing antioxidant capacity [54–56]. However, to date, only one study has evaluated the effects of a soy-containing diet in NAFLD patients. In a randomized, parallel clinical trial, 45 subjects with NAFLD were allocated to consume one of three different diets: a low-calorie diet (200–500 cal lower than required for each participant) (group 1); a low-calorie, low-carbohydrate diet (200–500 cal deficit; 45% kcal as carbohydrate, 35% kcal as fat, 20% kcal as protein) (group 2); or a low-calorie, low-carbohydrate soy-containing diet (similar to group 2 except in this diet 30 g of soy nut replaced 30 g of red meat) (group 3) [57]. NAFLD in patients was confirmed by sonography, and elevated serum levels of ALT and AST (>30 in men and >20 in women). After 8 weeks of the intervention, BMI, serum triglyceride, total cholesterol, ALT, AST and fibrinogen were significantly reduced while HDL-C increased in all three groups. Overall, all groups saw improvements in NAFLD grading. However, in those consuming the soy diet (group 3) there were greater reductions in serum fibrinogen, hs-CRP, malondialdehyde (MDA) and ALT compared to the other two groups. Changes in the serum AST were marginally significant and greatest in the soy diet group. Additionally, serum insulin levels decreased only in the soy diet group [57].

3.6. Curcumin

For hundreds of years, curcumin, an orange-yellow pigment present in the *Curcuma longa* L. (turmeric) has been used in Asian countries as a food spice [58]. Currently, curcumin has attracted significant attention as a natural polyphenol, due to reported anti-tumor, anti-inflammatory, antioxidant, antithrombotic, chemosensitizing and chemopreventive, anti-atherosclerotic and cardioprotective, lipid-modifying, analgesic, pulmonoprotective, antidepressant, and antirheumatic activities [59–79]. Beneficial effects of curcumin in metabolic syndrome and its determinants have also been observed (e.g., insulin resistance, obesity, hypertriglyceridemia, hypertension) [59]. This is thought to be related to curcumin's lipid-modifying, antioxidant, anti-inflammatory, insulin-sensitizing, anti-steatotic, and anti-fibrotic properties [80]. Therefore, it is not surprising that curcumin has become the subject of a growing body of evidence in the treatment of NAFLD. In addition to several animal studies [81,82], the utility of curcumin in human NAFLD has been tested with clinical trials. In a randomized controlled trial, 102 NAFLD patients (confirmed by liver sonography) were divided into two groups and treated with either 1000 mg curcumin per day in two divided doses (intervention group) or placebo (lactose, control group) for 8 weeks [64,83]. Additionally, all patients were advised on how to follow a healthy lifestyle throughout the study. After 8 weeks, serum total cholesterol, non-HDL-C, LDL-C, HDL-C, TG, ALT, AST and uric acid were significantly reduced with curcumin treatment, while in the

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control group total cholesterol, non-HDL-C, LDL-C, ALT, AST and uric acid were significantly increased. Furthermore, BMI, WC, fasting plasma glucose, and HbA1C were significantly reduced in both groups, although no significant changes were observed in serum insulin, HOMA-IR, HOMA-β and QUICKI either group. Comparing changes between the study groups showed significant differences in BMI, WC, serum total cholesterol, non-HDL-C, LDL-C, TG, ALT, AST and uric acid. Moreover, an improvement in ultrasonographic findings was observed in 75% of patients in the intervention group, while this rate was only 4.7% among the control group. No adverse events were reported in the study participants after consumption of curcumin [64,83].

In another clinical trial, 80 NAFLD patients (confirmed by ultrasonography) were randomized to be treated with an amorphous dispersion curcumin formulation (500 mg/day equivalent to 70 mg curcumin) or a matched placebo for 8 weeks [84]. At post intervention, BMI, serum total cholesterol, ALT, AST and HbA1c were significantly decreased and HDL-C notably increased among patients who received curcumin. Serum total cholesterol, LDL-C and fasting blood glucose were significantly increased in the placebo group. Comparing biochemical parameters between curcumin and placebo groups showed significant differences which all favored the intervention in serum total cholesterol, LDL-C, TG, BMI, ALT, AST, glucose and HbA1c. Furthermore, a significant improvement was found in liver ultrasonographic findings in the curcumin group (improvement in 78.9% of subjects) compared with placebo group (improvement in 27.5% of subjects). One case of stomach ache and two cases of combined stomach ache and nausea without no severe events were reported in the curcumin-treated patients [84].

3.7. Licorice root

Licorice is a plant of ancient origin, which is popular in both traditional and herbal medicine [85]. Glycyrrhizin is the principal component of licorice root extract [85]. Anti-inflammatory, antioxidant and immune-modulating activities, spasmolytic, laxative, anti-depressive, anti-ulcer, anti-diabetic and hepato-protective responses were reported as beneficial properties of this plant [85,86]. However, using high amounts of glycyrrhizin could result in hypermineralcorticoid-like effects in both animals and humans [85]. It has been previously proposed that licorice would display therapeutic effects on liver diseases since it was shown to reduce liver inflammation and hepatic injury in earlier studies [85–88]. To evaluate the efficacy of licorice root extract in NAFLD patients, a randomized controlled trial was recently conducted [89]. Using sonography to confirm NAFLD, 66 patients with elevated serum ALT and AST were assigned to either consume 2 g of an aqueous licorice root extract per day or a placebo (2 g starch/d) for 2 months. At the end of the intervention, BMI did not significantly change in either of the groups. However, serum ALT and AST significantly decreased only in the licorice group compared to baseline. No side effects were observed in this study [89].

3.8. Olive and canola oils

It has been shown that adherence to a Mediterranean-style diet is associated with a lower prevalence of non-communicable diseases such as CVD, certain types of cancers and hepatic disorders [90,91]. Olive oil, with high amounts of monounsaturated fatty acids (MUFA) and antioxidant phenolic compounds, is considered as a major constituent of the Mediterranean diet [91]. It is proposed that olive oil can cause reductions in accumulation of TG in the liver, improvements in postprandial TG, glucose and glucagon-like peptide-1 responses in insulin-resistant subjects and upregulate glucose transporter-2 expression in the liver [92]. These effects are thought to be mediated through several mechanisms including reducing nuclear factor-kappaB activation, decreasing LDL oxidation, and improving insulin resistance by reducing the production of pro-inflammatory cytokines (tumor necrosis factor, interleukin-6) (62). Another vegetable oil with high concentrations of MUFA is canola oil, and its therapeutic properties in lowering blood lipids has been reported previously [93,94]. In a clinical trial, 93 adult males (NAFLD diagnosed by ultrasound) were randomized into one of three groups receiving either olive oil, canola oil, or a commonly used soybean/safflower oil (control group) as a cooking medium (not exceeding 20 g/day) for 6 months [95]. At post intervention, BMI decreased significantly in those assigned to the olive oil group compared to the control group. Additionally, fasting insulin and HOMA-IR were significantly decreased in both the olive and canola oil groups compared to control. However, serum ALT and AST activities decreased non-significantly in all three groups. The severity of fatty liver significantly decreased from baseline in the olive and canola oil groups but was unchanged in the control group. After the intervention, 66.7% of the patients in the olive oil group and 76.7% of the patients in the canola oil group reverted to normal liver grading, and these were significantly greater changes than the control group [95].

3.9. Soluble fibers

The health benefits of fibers, particularly soluble fibers, in prevention of chronic diseases such as coronary heart disease, stroke, hypertension, diabetes, obesity and certain gastrointestinal diseases have been well-known [96]. Consumption of soluble fibers have been reported to improve blood lipids and blood pressure, increase insulin sensitivity, and decrease the prevalence of CVD [96]. Since metabolic abnormalities, notably obesity and dyslipidemia, are the relevant risk factors for NAFLD [97], soluble fibers may be considered as a protective agent in the treatment of NAFLD. In this regard, Rocha et al. [68] conducted a clinical trial, on which 12 NAFLD patients included using Imaging methods (ultrasonography or computed tomography or magnetic resonance imaging), showing hepatic steatosis and elevated ALT and AST to diagnose NAFLD. Patients were asked to consume 10 g of soluble fiber with no added sugar, distributed in two doses of 5 g, 30 min before of their main meals. After 3-months intervention, the mean of BMI and waist circumference, serum glucose and HOMA values decreased non-significantly and serum TG and cholesterol increased non-significantly. However, ALT and AST significantly decreased, while GGT tended to decrease. Diarrhea as a side effect of the treatment caused one patient to drop out of the study [98].

3.10. Xuezhikang

In Chinese traditional medicine, Xuezhikang has been widely applied to treat cardiovascular diseases [99,100]. Xuezhikang, which is extracted from red yeast rice, has high concentrations of naturally-occurring lovastatin and its homologues, as well as unsaturated fatty acids, flavonoids, plant sterols and other biologically active constituents [99,100]. It has been reported that Xuezhikang improves the blood lipids profile, through lowering serum TG, total cholesterol, LDL-C and increasing HDL-C [101–103]. Xuezhikang also appears to improve liver health by inhibiting hepatic fat accumulation [73]. The efficacy of Xuezhikang in the treatment of NAFLD was previously assessed in a clinical trial [104]. In this study, 84 confirmed NAFLD patients with hyperlipidemia (total cholesterol $\geq$5.72 mmol/L and/or TG $\geq$1.70 mmol/L), were randomized and treated for 24 weeks with either two Xuezhikang capsules per day (0.3 g per capsule and 2.5 mg of lovastatin [intervention group]) or three control capsules per day (228 mg polyene phosphatidylcholine from soybean per capsule [control group]). Compared to baseline, serum ALT, AST, and cholinesterase (CHE)

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were significantly reduced in both groups after both 12 and 24 weeks. However, the reductions in ALT and CHE after 12 weeks were significantly greater in the control group compared to the intervention group. After 12 weeks, the treatment group had significantly greater reductions in serum TG and increases in HDL-C compared to the control group. In the treatment group, diarrhea was reported by one patient which caused them to drop out of the study [104].

3.11. Qianggan

Qianggan, another Chinese herbal medicine, consists of 16 Chinese herbs and has been suggested as a useful treatment for liver disease [105–107]. For example, components of Qianggan such as *Radix Salviae Miltiorrhiza*, *Radix Angelica Sinensis*, and *Radix Astragalus Membranaceus* have been previously reported to have anti-fibrotic properties [105]., Li et al. [78] conducted a randomized controlled trial to evaluate the efficacy of Qianggan in the treatment of NAFLD. In this study, 88 NAFLD patients were recruited and randomly assigned to receive either Qianggan capsules (treatment group) or polyene phosphatidylcholine capsules (PPC)(control group) for 6 months. The 6-month regimen for the treatment group involved three capsules of Qianggan taken in the morning, three at noon and four in the evening, with a one-day pause after every six days; for the control group, two PPC capsules (228 mg PPC per capsule) were taken three times a day. After 6 months, the Qianggan-treated group significantly increased the CT liver/spleen ratio, while this was not observed with the control. In addition, serum ALT levels were reduced in the intervention group to a greater extent than the control group. However, no significant changes were observed in serum AST, GGT or total cholesterol. Nausea, burning sensation, and diarrhea were reported by some subjects in the treatment group, however, the incidences of these adverse reactions were not significantly different compared to the control group [108].

3.12. Chlorella

Chlorella, a type of unicellular green algae, is considered a functional food due to its high content of amino acids, minerals, vitamins and fiber [109–111]. One the most well-known strains of chlorella, *Chlorella vulgaris* (*C. vulgaris*), contains phytochemicals of medicinal interest, such as chlorophyll, tocopherols, and ubiquinone [109,112,113]. *C. vulgaris* has been widely used as a nutritional supplement with a good record of safety, especially for the prevention and treatment of several metabolic disorders (e.g., dyslipidemia, hyperglycemia, hypertension, obesity) [114]. It has also been suggested that *C. vulgaris* may decrease fasting plasma glucose through the activation of insulin signaling pathways [114]. Considering its favorable effects on both insulin resistance and lipid metabolism, it has been proposed that *C. vulgaris* might be effective in the treatment of NAFLD. In a randomized controlled trial, 70 NAFLD patients (confirmed by ultra-sonography) were divided into two groups to receive either *C. vulgaris* (300 mg daily) (intervention group) or placebo (control group) for 8 weeks [114]. Compared to baseline, weight and WC significantly decreased in both groups, however, the intervention group lost significantly more weight compared to the control group. Both fasting serum glucose and TNF-α were significantly reduced in the *C. vulgaris* group compared to control group. Serum ALT, AST, insulin, HOMA-IR and hs-CRP were significantly reduced in the *C. vulgaris* group over time, although differences between groups were not statistically significant. No adverse effects were reported by the intervention participants [114].

In another study, 60 NAFLD patients (confirmed by ultrasonography and elevated serum liver enzymes) were randomized into two groups and treated with either 400 mg/day of vitamin E plus 1200 mg of *C. vulgaris* daily or 400 mg/day of vitamin E and placebo tablets for 8 weeks [115]. At the end of the study, the C. vulgaris-treated group displayed significantly greater reductions in body weight, BMI, serum ALP and fasting blood glucose compared to the control group [115].

In another randomized clinical trial, 76 NAFLD patients were divided in two groups: 1) a Chlorella-treated group, who was given *C. vulgaris* extract (1200 mg/day) + metformin (750 mg/day) + vitamin E (200 mg/day) for 3 months, and 2) a metformin-treated control group, who received metformin (1250 mg/day) + vitamin E (200 mg/day) for 3 months [116]. Post intervention, both groups had significant reductions in body weight and BMI. In the Chlorella-treated group, significant reductions were observed for serum ALT, AST, TG, uric acid, HbA1c and HOMA-IR index, however, these parameters were not significantly different compared to the metformin-treated control group. In this study, some patients dropped out due to side effects [116].

3.13. Danning Pian

Danning Pian is a compound traditional Chinese medicine, composed of various medicinal herbs, which is used to treat cholecystitis and prevent the formation of gallstones [117–119]. It has been reported that Danning Pian has similar properties as ursodeoxycholic acid (UDCA) [120], which is widely used in treatment of liver diseases [121,122]. UDCA may decrease the production of hydrophobic bile acids, which are known to increase cellular damage and oxidative stress in hepatocytes; therefore, UDCA has been suggested to protect against liver injury in NAFLD patients [123]. Furthermore, it is proposed that UDCA may increase insulin sensitivity by decreasing TNF-α in NAFLD patients [124]. However, since Danning Pian is less expensive compared to UDCA and easily obtainable [120], there has been interest in the potential for this traditional Chinese medicine in the treatment of NAFLD. In one trial study, 232 NAFLD patients after confirmation by CT and/or B ultrasonography received 5 tablets of Danning Pian orally thrice daily for three months, in addition to following healthy lifestyle, balanced diet and physical exercise [120]. If the patients suffered from diarrhea, the dose was changed to 3 tablets orally thrice daily or 5 tablets orally twice daily. Yiganling Pian (77 mg, tid), compound vitamin B (2 Tab, tid), vitamin E (20 mg, tid) or others were also given to some of the patients. Serum ALT was decreased significantly after the intervention among patients. Serum AST, GGT, ALP and bile acid were also improved to some extent after intervention. Serum TG but not total cholesterol was significantly decreased at the end of the study among individuals who had elevated TG at baseline. Pathological changes of fatty liver confirmed by ultrosonograghy showed that fatty liver was ameliorated in 34% of patients (79/232). Danning Pian therapy had no effects on body weight, waistline and blood sugar of the patients. Adverse events were seen in 15.1% (35/232) patients. The most frequent adverse events were diarrhea followed by nausea, elevated ALT and skin rash [120]. In a double-blinded controlled trial, 135 patients with NAFLD were randomly divided into two groups and given either Dannin Pian or UDCA for 24 weeks (95). The first group (n = 102) received 5 Danning tablets (DNT) three times per day (4.45 g of concentrated herbal extract per tablet). The second group (n = 33) was given 250 mg UDCA three times per day. After 24 weeks of the intervention, mean BMI and main symptom score (debilitation and anorexia) were significantly reduced in the DNT-treated group compared to the UDCA-treated group. Serum ALT, AST, GGT and TG were significantly reduced in both groups, while differences between groups were not significant. Liver B-scan ultrasound and CT images showed both DNT and UDCA were effective in improvement of NAFLD histological features. Diarrhea was common in the

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DNT-treated group, although this was reduced by lowering the dosage. Nausea (3 patients) and skin rash (1 patient) were also observed with DNT-treatment [125].

3.14. Yiqi Sanju

Another Chinese herbal medicine with potential to in the treatment of NAFLD is Yiqi Sanju Formula (YQSJF). YQSJF consists of Pollen Typhae and several other Chinese herbs and has been investigated for the treatment of metabolic diseases such as type 2 diabetes [126]. It has been reported that YQSJF had favorable effects on central obesity, metabolic syndrome and its parameters in a clinical trial [127]. In another randomized control trial, the effect of YQSJF on the treatment of NAFLD was assessed [128]. In this study, a total of 60 NAFLD patients were divided into two groups to treat with either YQSJF (2 times/day) or a placebo for 3 months. In addition, all patients were given health education to follow a low-fat, calorie-controlled diet, and appropriate exercise regimen. After the 3 months of treatment, the CT ratio of liver-spleen was significantly improved and BMI, WCs, HOMA-IR, TG, total cholesterol, LDL-C, ALT, AST, TNF-α and hs-CRP were significantly decreased and HDL-C was notably increased compared with before treatment and these changes were statistically significant in comparison the YQSJF group compared to the placebo group. Likewise, NAFLD grade of patients were significantly improved in YQSJF group compared with placebo group. Mild diarrhea, gastrointestinal discomfort and reduced appetite were observed in 3 patients of the YQSJF group [128].

3.15. Bayberry

Bayberry, also known *Myrica*, is a subtropical evergreen fruit tree native to China and Southeast Asia. The high antioxidant capacity of bayberry *in vitro* is attributed to its anthocyanins and a variety of phenolic acids, including caffeic, ferulic, sinapic, and salicylic acids [129,130]. Furthermore, animal studies have shown that berries rich in anthocyanins and phenolic acids might be useful to improve NASH-related symptoms of oxidative stress, dyslipidemia, liver steatosis, and inflammation [131–133]. Due to these characteristics of bayberry, Guo et al. (104) investigated its effect on NAFLD markers in a randomized, placebo-controlled, double-blind, crossovertrial with 88 NAFLD patients [134]. Individuals with a BMI >23.1 kg/m^2 and met diagnostic criteria for NAFLD by ultrasonography were recruited to consume 250 mL of bayberry juice or placebo twice daily for 4 weeks each. At the end of study, no significant changes were seen with either arm of the study for anthropometric variables, plasma TG, TC, LDL-C, fasting glucose, insulin, HOMA-IR, ALT, AST and hs-CRP. However, the effect of bayberry juice on oxidative stress, inflammation, and apoptosis markers was favorable. Protein carbonyl groups (a serologic marker of oxidative stress), IL-8, TNF-α, cytokeratin-18 fragment M30 (an apoptosis marker) and tissue polypeptide-specific antigen (an apoptosis marker) were significantly reduced with bayberry juice compared to control. No adverse effects were reported by any of the study participants [134].

3.16. Dietary phospholipids

Essential phospholipids (EPL) is a term used for the natural mixture of polyenylphosphatidylcholine (PPC) extracted from soybeans [135]. This extract contains a high concentration of polyunsaturated phosphatidylcholines, of which 1,2-dilinoleoylphosphatidylcholine (DLPC) is particularly abundant compared to other natural sources of phospholipids and lecithin [135,136]. EPL, as a source of polyunsaturated phosphatidylcholine, may have positive effects on the cell membrane as well as anti-inflammatory, anti-fibrotic, and lipid-regulating effects [135,136]. Moreover, animal studies have suggested that DLPC could reduce lipid peroxidation, oxidative stress and hepatic fibrosis [136,137]. Due to these potential health benefits of EPL, it has been proposed that this compound may be a useful agent for the treatment of NAFLD. In this regard, a randomized clinical trial was conducted in 324 NAFLD patients diagnosed by clinical examination and laboratory tests [137]. Patients were randomized to one of three groups. In the first group, only patients with NAFLD without having any comorbid diseases were included. In the second group, NAFLD patients who had type 2 diabetes mellitus and were treated with metformin, pioglitazone or both for at least six months before enrolment were included. In the third group, NAFLD patients with mixed type hyper-lipidemia and were treated with atorvastatin, ezetimibe or both for at least six months before enrolment were included. All patients were received essential phospholipid (EPL) 1800 mg 6 capsules/day in 3 divided doses for 24 weeks followed by EPL 900 mg 3 capsules/day in 3 divided doses for another 48 weeks. In addition, all patients were advised to follow healthy diet and being physically active. Patients in the second and third groups took their prescribed drugs as stated above, only their prescribed drugs were adjusted if they reached to HgbA1C <6.5% or normalized blood lipid. Results of this showed that after the first six months intervention transaminases decreased in 80.5%, 84.1% and 87.5% of patients in patients of the first, second and third group, respectively. The mean reduction per patients were 54.6 IU, 44.9 IU and 52.9 for ALT and 48.7 IU, 40.5 IU and 49.2 IU for AST, respectively in the first, second and third groups. A slight rise of the transaminases over the next three months was observed after dose reduction to 900 mg per day. After that it again started to decrease and it maintained in a significant normal range or only above the upper limit of normal. In the NAFLD patients with diabetes mellitus type 2 and hyperlipidemia, a non-significant better response to EPL treatment were observed. In addition, a slight improvement in ultrasound findings was observed in the three treatment groups. Moreover, elastography examination showed that an improvement in liver stiffness measurement in 14.2%, 26.1% and 20.2% of patients in NAFLD lone, NAFLD with diabetes mellitus type 2 and NAFLD with hyperlipidemia, respectively [137].

3.17. Resveratrol

Resveratrol is a natural polyphenol found in a variety of plants and spices. Grapes, peanuts, berries, and red wine are the richest sources of resveratrol in the typical human diet [138]. Tissue damage to the liver, kidney, and brain caused by oxidative stress and inflammation may be neutralized due to the antioxidant and anti-inflammatory activities of resveratrol [139]. Therefore, it may be beneficial in attenuating or preventing the progression of several diseases related to oxidative stress and inflammation, including cancer, CVD, diabetes, and other metabolic diseases [140–144]. The therapeutic efficacy of resveratrol in NAFLD patients was investigated recently by Faghihzadeh et al. [126,127]. In a randomized, double-blinded, controlled clinical trial, 50 NAFLD patients (confirmed by ultrasonography) were assigned to consume as capsules either 500 mg trans-resveratrol per day (intervention group) or 500 mg medium-chain TG per day (control group) for 12 weeks. All participants were advised to consume an energy-balanced diet and follow physical activity recommendations [145,146]. At the end of the study, serum ALT, TNF-α, IL-6, cytokeratin-18 M30, peripheral blood mononuclear cell NF-κB activity, hepatic tissue echogenicity assessed by ultrasound, and hepatic steatosis grade were significantly reduced in the resveratrol-treated group compared to the control group. Moreover, no notable adverse effects were reported by the study patients [145,146].

In another double-blind, randomized, placebo-controlled trial, 60 patients with NAFLD (confirmed by ultrasound) were assigned to either an intervention group which consumed two 150 mg resver-

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atrol capsules twice daily for 3 months (resveratrol group) or a control group, in which individuals received two placebo capsules twice daily for the duration of the study (placebo group) [147]. After the intervention period, significant improvements were observed in the resveratrol group for serum AST, ALT, fasting glucose, total cholesterol, LDL-C and HOMA-IR in the compared to the placebo group. Additionally, resveratrol significantly reduced the serum concentrations of TNF-α, cytokeratin 18 fragment, and fibroblast growth factor 21 and increased adiponectin compared to placebo [147]. However, there were no significant differences between groups for changes in the severity of hepatic fatty infiltration assessed by ultrasound. No adverse events were reported by patients in the study [147].

A recent placebo-controlled, randomized clinical trial evaluated the effectiveness of high-dose of resveratrol for the treatment of NAFLD [148]. In this study, a total of 28 biopsy-verified NAFLD patients were randomized into either a placebo group (n = 13) or a group receiving 1.5 g resveratrol daily for 6 months (n = 15). Compared to placebo, patients treated with resveratrol had no significant differences for changes in serum bilirubin, ALP, ALT, AST, CD163 and TNFα (as markers of NAFLD severity and inflammation), body weight, markers of glucose homeostasis, serum cholesterol profile, and NAFLD severity measures (intrahepatic lipid content, histology). However, serum GGT, serum TG and diastolic blood pressure were notably improved with resveratrol treatment compared to placebo. Gastrointestinal side effects occurred with resveratrol treatment as well as a serious case of febrile leukopoenia and thrombocytopenia that developed after 10 days of resveratrol treatment [148].

3.18. Anthocyanin

Anthocyanins are water-soluble pigments which contribute to the red, purple and blue colors of many flowers, cereal grains, fruit, and vegetable [149]. Anthocyanins are also highly bioactive compounds that belong to the flavonoid subclass of polyphenols [119]. Berry fruits, including blackberries, blueberries, and strawberries, are considered one of the richest food sources of anthocyanins [150]. Anthocyanins have been reported to display antioxidant activities directly, enabling them to scavenge reactive oxygen species and free radicals, and also modulate endogenous antioxidant defense, which may all contribute to a prevention of oxidative stress [149]. Recently, several health benefits were attributed to anthocyanins as dietary bioactives, including obesity and diabetes control, CVD prevention, and improvement of visual and brain functions [150,151]. Furthermore, a positive role of anthocyanins in the modulation of lipid metabolism and fat deposition in the liver and several other tissues, as well as attenuations in hyperglycemia and inflammation has been documented [149,150]. In a randomized controlled trial, 74 NAFLD patients who were diagnosed using ultrasound, were recruited to consume either 320 mg/day of purified anthocyanins derived from bilberry and black currant (4 capsules, each capsule contained 80 mg anthocyanins) or receive a placebo for 12 weeks [152]. At the end of the intervention, there were no notable effects on BMI, WC, blood pressure, serum AST, NAFLD fibrosis score, total cholesterol, LDL-C or insulin. However, compared with placebo, treatment with anthocyanins significantly reduced serum ALT, cytokeratin-18 M30 fragment and myeloperoxidase concentrations (indicator of inflammation and oxidative stress). The intervention was without any side effects [152].

3.19. Garlic

Garlic, considered by some as a functional food, has been widely used as an herbal remedy for thousands of years [153]. This well-known plant contains several bioactive compounds, including unique water and lipid-soluble organosulfur compounds, such as allicin, as well as flavonoids which contribute antioxidant properties. Since it contains several phytochemicals with known antioxidant activities, garlic may neutralize reactive oxygen species (ROS) and prevent oxidative damage [154]. Previous studies have reported beneficial effects of garlic in the reduction of some types of cancer, as well as prevention of CVD due to effects on blood pressure, hypercholesterolemia [153,155]. Furthermore, in vitro studies report that garlic has anti-diabetic, anti-obesity, anti-atherosclerotic, anti-carcinogenic and anti-thrombotic properties, although in vivo studies are required to confirm these effects [153,155]. Considering its potential application to human health, few side effects and low cost, garlic appears to be a promising functional food for NAFLD [153]. Hepatic oxidative stress is considered one of the main features of NAFLD pathogenesis [8]. Thus, because of the antioxidant capacity of garlic, its efficacy in the treatment of liver disease was recently assessed in both animal and human studies [156–158]. In a randomized controlled trial, 110 NAFLD patients (confirmed by ultrasonography) with elevated serum ALT and AST were assigned to consume either 400 mg of garlic powder tablets (two tablets, consumed after breakfast and dinner daily) (intervention group) or placebo tablets (control group) for 15 weeks [159]. Comparison of changes between groups revealed that changes in both body weight and body fat were significantly greater in the intervention group compared with placebo group. However, in the results of this study, other factors such as clinical and biochemical parameters were not reported. No adverse effects were observed in this study [159].

3.20. Berberine

Berberine is an isoquinoline alkaloid, derived from natural plants [160]. Several biological activities have been attributed to this herb as well as favorable effects on various metabolic disorders [161]. It has been shown that berberine has anti-hyperglycemic, anti-dyslipidemic effects and it could also reduce hepatic steatosis [162]. The positive effect of berberine in treatment of NAFLD has recently been determined by systematic review and meta-analysis studies [161,163]. The possible mechanisms that berberine inhibits NAFLD progression include increasing insulin sensitivity, regulating AMP-activated protein kinase (AMPK), improving mitochondrial function, reducing oxidative stress, and regulating gut microenvironment [164]. The efficacy of this compound in the treatment of NAFLD has been investigated in several clinical trials. In a randomized, controlled, open-label parallel design clinical trial, 184 NAFLD patients confirmed by proton magnetic resonance spectroscopy (1H MRS) were enrolled and divided into three intervention groups and followed for 16 weeks [165]. The first group received a lifestyle intervention (dietary modification and exercise regimen), the second group treated with lifestyle intervention plus 15 mg pioglitazone (PGZ) per day, and a third group treated with lifestyle intervention plus 0.5 g berberine three times per day and taken 30 min before a meal. Compared to lifestyle intervention alone, the addition of berberine significantly reduced body weight, BMI, WC, hepatic fat content (via 1H MRS), serum total cholesterol, TG, apolipoprotein B, ALT and AST. Furthermore, reductions in weight, BMI, WC, serum total cholesterol and TG were significantly greater in the lifestyle intervention plus berberine group compared to the lifestyle intervention plus pioglitazone group. Reductions in hepatic fat content also tended to be greater with berberine treatment compared to pioglitazone. Overall, the efficacy of a lifestyle intervention plus berberine in reducing NAFLD-related biomarkers was similar, if not superior, to a lifestyle intervention plus pioglitazone treatment. Anorexia and upset stomach, diarrhea, and constipation were the main adverse events in the subjects in the

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Table 1
Studies on herbal bioactive compounds in treatment of non-alcoholic fatty liver disease (NAFLD).

Author, Year	Agent	Dose	Treatment duration	Inclusion criteria	Number of participants	Mean age	Intervention assigned to control group	Method of steatosis assay	Main finding on liver fat
Yari Z et al. 2016 [28]	Flaxseed + life style modification	30 g/d	12 weeks	NAFLD[†]	50	45.02	Lifestyle modification	Fibroscan	In flaxseed group, 46% had a 1-level and 12% had 2-level reduction in steatosis score, but no grade reduction was observed in control group. Fibrosis score significantly decreased in intervention group compared to control.
Askari F et al. 2013 [35]	Cinnamon	1500 mg/d	12 weeks	NAFLD	50	≃[‡]42.42	Placebo capsules (wheat flour)	NM [≠]	NM
Sakata R et al. 2013 [36]	Green tea (catechins)	700 mL green tea (1080 mg catechins)/d or 700 mL green tea (200 mg catechins)/d	12 weeks	NAFLD	17	≃50.9	Green tea-flavored beverage (contained 0 mg catechins)	Ultrasonography and CT[#]	Liver-to-spleen CT attenuation ratio increased from 91.8 ± 4.6% (baseline) to 101.8 ± 4.7% in 1080 mg catechins group. Improvement in liver-to-spleen CT attenuation ratio among 1080 mg catechins group was greater compared to other groups.
Pezeshki A. et al. 2016 [45]	Green tea	500 mg green tea extract/day	12 weeks	NAFLD	80	20–50 years	Placebo tablets contained pure microcrystalline cellulose	NM	NM
Abenavoli L et al. 2015 [48]	Silymarin/silybin	G[*]1: MD[±] G2: MD+ silybin 184 mg, phosphatidylcholine 388 mg, vitamin E acetate 50% 178.56 mg	6 month	NAFLD	30	G1:56[**] G2:46 G3:33	No treatment	Ultrasound	Hamaguchi score[a] significantly reduced in both G1 and G2. FLI[b] significantly reduced in G1 and G2 compared to control group.
Loguercio C 2012 [49]	Silymarin/silybin	silybin 188 mg, phosphatidyl-choline 388 mg, vitamin E acetate 50% (178.56 mg)	12 month	NAFLD	179	≃42.5	Placebo (extra white saccharine replacing active component)	Ultrasound	No significant improvement seen on degree of liver steatosis

Table 1 (*Continued*)

Author, Year	Agent	Dose	Treatment duration	Inclusion criteria	Number of participants	Mean age	Intervention assigned to control group	Method of steatosis assay	Main finding on liver fat
Federico A et al. 2006 [50]	Silymarin/silybin	376 mg of silybin, 776 mg of phosphatidylcholine, and 360 mg of vitamin E	6 month	NAFLD	85	NM	Not treated	Ultrasound	Steatosis, graded from 0 to 3, significantly improved in NAFLD treated group compared with control group.
Aller R et al. 2015 [51]	Silymarin/Silybin	Silybum 1080.6 mg plus 72 mg vitamin E+ hypocaloric diet	3 month	NAFLD	36	47.4	Hypocaloric diet	Biopsy	NAFLD-FS[c] and FLI significantly reduced in both groups compared with baseline. LAP[d] did not significantly change in any groups.
Sorrentino G et al. 2015 [52]	Silymarin/Silybin	250 mg of silibinin and 30 IU of vitamin E	3 month	NAFLD	78	≃56	Not treated	Ultrasound	Significant greater reductions observed in right liver lobe (cm), HSI[e], LAP of treated patients than control subjects
Hashemi Kani A et al. 2013 [57]	Soy	G1: low-calorie, low-carbohydrate diet + 30 g soy	8 weeks	NAFLD	45	G1:45.6 G2:49.3 G3:48.5	G2: low-calorie diet G3: low-calorie, low-carbohydrate diet	Sonography	15 patients with grade 1 and 2 NAFLD at baseline in all groups, in each group, 5 changed to a healthy status at end of trial
Panahi Y et al. 2017 [83]	Curcumin	1000 mg curcumin/d	8 weeks	NAFLD	102	≃46	Placebo (lactose)	Ultrasound	Ultrasonographic findings were improved in 75.0% of subjects in curcumin group, while rate of improvement in control group was 4.7%
Rahmani S et al. 2016 [84]	Curcumin	500 mg/d an amorphous dispersion curcumin formulation equivalent to 70-mg curcumin	8 weeks	NAFLD	80	≃47.66	Placebo	Ultrasound	Improvement in 78.9% of subjects of intervention group compared with 27.5% of patients in placebo group
Hajiaghamohammadi et al. 2012 [89]	Licorice root	2-g aqueous licorice root extract/d	2 month	NAFLD	66	≃40.2	Placebo (2-g starch/d)	NM	NM

Table 1 (*Continued*)

Author, Year	Agent	Dose	Treatment duration	Inclusion criteria	Number of participants	Mean age	Intervention assigned to control group	Method of steatosis assay	Main finding on liver fat
Nigam P et al. 2013 [95]	Olive and canola oils	Olive (G1) or canola (G2) oils not exceeding 20 g/d	6 month	NAFLD	93	G1:37.2 G2:38.0 G3:63.2	Soybean/safflower oil (G3) (not exceeding 20 g/d)	Ultrasound	66.7% of patients in G1 and 76.7% of patients in G2, reverted to normal liver grading which were significantly higher than G3.
Rocha R et al. 2007 [98]	Soluble fibers	10 g of soluble fiber	3 month	NAFLD	12	40.3	–	NM	NM
Xiao-fen F et al. 2010 [104]	Xuezhikang	0.6 g Xuezhikang and 5 mg of lovastatin/D	24 weeks	NAFLD	84	≃54.45	0.684 g polyene phosphatidyl-choline/d	NM	NM
Li L et al. 2010 [108]	Qianggan	10 capsules/d	6 month	NAFLD	88	≃48.2	1368 mg phos-phatidylcholine	CT[f]	Significant increase observed in CT liver/spleen ratio in intervention groups and was significantly greater compared to control
Ebrahimi-Mameghani M, et al. 2016 [114]	Chlorella	1200 mg chlorella vulgaris/d	8 weeks	NAFLD	70	≃37.36	Placebo	NM	NM
Ebrahimi-Mameghani M, et al. 2014 [115]	Chlorella	400 mg/d vitamin E plus 1200 mg Chlorella vulgaris	8 weeks	NAFLD	60	≃37.36	400 mg/d vitamin E and placebo tablets	NM	NM
Panahi Y et al. 2012 [116]	Chlorella	Chlorella vulgaris extract (1200 mg/d) +metformin (750 mg/d) +vitamin E (200 mg/d)	3 month	NAFLD	76	≃49	Metformin (1250 mg/d) +vitamin E (200 mg/d)	NM	NM
Fan JG. 2004 [120]	Danning Pian	5 tablets of Danning Pian orally thrice daily	3 month	NAFLD	232	46.1	–	Ultrosound	Fatty liver ameliorated in 34% of patients (79/232).
Guang JI et al. 2008 [125]	Danning Pian	Danning tablets contained concentrated herbal extract consisting of 66.75 g/d	24 weeks	NAFLD	135	≃47	750 mg eoxycholic acid	B-ultrasound and CT	Improvement in B-ultrasound and CT images was observed in both groups, however, no significant changes between groups
Lou SY et al. 2008 [128]	Yiqi Sanju	2 times/day	3 month	NAFLD	60	≃53.7	Placebo	CT	CT ratio of liver-spleen and NAFLD grade of patients were significantly improved in treatment group compared to placebo group

Table 1 (*Continued*)

Author, Year	Agent	Dose	Treatment duration	Inclusion criteria	Number of participants	Mean age	Intervention assigned to control group	Method of steatosis assay	Main finding on liver fat
Guo H et al. 2014 [134]	Bayberry	500 mL of either bayberry	4 weeks	NAFLD	88	21.2	Placebo (bayberry-flavored placebo beverage)	NM	NM
Dajani A et al. 2015 [137]	Essential phospholipid (EPL)	G1: 1800 mg EPL (24 weeks) +900 mg EPL (48 weeks follow-up)	24 weeks + 48 weeks follow-up	G1: NAFLD G2: T2DM NAFLD G3: Hyperlipidemia NAFLD	324	G1 = 46.8 G2 = 42.6 G3 = 40.9	G2: 1800 mg EPL (24 weeks) + 900 mg EPL (48 weeks follow-up) plus metformin and/or pioglitazone. G3: 1800 mg EPL (24 weeks) +900 mg EPL (48 weeks follow-up) plus atorvastatin and/or ezetimibe	Elastography	Improvement in liver stiffness measurement seen in 14.2%, 26.1% and 20.2% of patients in NAFLD alone, NAFLD with diabetes mellitus type 2 and NAFLD with hyperlipidemia, respectively.
Faghihzadeh F et al. 2014 [145]	Resveratrol	500 mg trans-resveratrol capsule	12 weeks	NAFLD	50	≃45.16	500 mg placebo capsule (medium-chain triglyceride)	Ultrasound	Hepatic tissue echogenicity and hepatic steatosis grade significantly reduced among resveratrol group compared to control group
Chen S et al. 2015 [147]	Resveratrol	Two 150 mg resveratrol capsules/d	3 month	NAFLD	60	44.3	Two placebo capsule/d	Ultrasound	No significant changes observed between groups in severity of hepatic fatty infiltration
Heebøll S et al. 2016 [148]	Resveratrol	1.5 g resveratrol daily	6 month	NAFLD	28	NM	Placebo	Biopsy	No significant changes were seen in histological changes regarding steatosis, inflammation, ballooning or fibrosis
Zhang PW et al. 2015 [152]	Anthocyanins	320 mg/day purified anthocyanins	12 weeks	NAFLD	74	≃45.9	Placebo capsules contained maltodextrin and blue color	Ultrasound	Intervention with anthocyanins had no notable effect on NAFLD fibrosis score

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Table 1 (*Continued*)

Author, Year	Agent	Dose	Treatment duration	Inclusion criteria	Number of participants	Mean age	Intervention assigned to control group	Method of steatosis assay	Main finding on liver fat
Soleimani D et al. 2016 [159]	Garlic	400 mg garlic powder tablets (coated tablets contain 1.5 mg allicin)	15 weeks	NAFLD	110	45.2	Placebo tablets (coated tablets contain starch and microcrystalline cellulose)	NM	NM
Yan MH el. 2015 [165]	Berberine	G1: lifestyle intervention plus 1.5 g berberine/d	16 weeks	NAFLD	184	≃55	G2: lifestyle interventiong3: lifestyle intervention plus pioglitazone (PGZ) 15 mg qd	Proton magnetic resonance spectroscopy	Treatment with lifestyle intervention plus berberine caused greater reduction in hepatic fat content compared to lifestyle intervention alone. Similar efficacy of berberine treatment with pioglitazone treatment.
Chen S et al. 2015 [172]	Dihydromyricetin	Two 150 mg dihydromyricetin capsules twice daily	3 month	NAFLD	60	45.1	Two 150 mg placebo capsules twice daily	Ultrasound	Treatment with dihydromyricetin had no significant effect on severity of fatty infiltration
Wong VWS et al. 2013 [174]	Phyllanthus	1 g Phyllanthus urinaria (two tablets) three times daily	24 weeks	NASH[§]	60	≃50	Phyllanthus-like placebo two tablets three times daily	Biopsy	No notable changes found in activity score, steatosis percentage, steatosis grade and fibrosis in Phyllanthus group compared to placebo group.

[†]Non-alcoholic fatty liver disease.
[‡]Average of ages of intervention and control groups.
[≠] Not mentioned.
[#]Computed tomography.
[*]Group.
[±]Mediterranean diet.
[**]Median.
[a]Showing the hepatic fat accumulation grade using ultrasound examination.
[b]Fatty liver index.
[c]NAFLD-Fibrosis score.
[d]Liver accumulation product.
[e]Hepatic Steatosis Index.
[f]Computerized tomography.
[§]Non-alcoholic steatohepatitis.

Table 2
Adverse effect of herbal bioactive nutrients in treatment of non-alcoholic fatty liver disease (NAFLD).

Therapeutic agents	Side effects
Flaxseed	No serious side effect [28].
Cinnamon	Not mentioned [35].
Green tea	No side effect [36], Not mentioned [45].
Silymarin/Silybin	No adverse effect [48], [50], [51], [52], transient diarrhea, dysgeusia, and pruritus [49].
Soy	Not mentioned [57].
Curcumin	No adverse events [83]. One case with stomachache and two cases with combined stomachache and nausea with no severe events [84].
Licorice	No side effect [89].
Olive and canola oil	Not mentioned [95].
Soluble fiber	Diarrhea was seen on one patient [98].
Xuezhikang	Diarrhea was reported by a patient [104].
Qianggan	Nausea, burning sensation and Diarrhea were observed in a few of subjects [108].
Chlorella	No adverse effect [114], Not mentioned [115], some unacceptable side effects [116].
Danning Pian	diarrhea followed by nausea, elevated ALT and skin rash [120], diarrhea, reduced by discounting intervention. Nausea and skin rash were the other adverse effects [125].
Yiqi Sanju	Mild diarrhea, gastrointestinal discomfort and reduced appetite [128].
Bayberry	No adverse effect [134].
Essential phospholipids	Not mentioned [137].
Resveratrol	No notable adverse effects were reported by the study patients [145,146] [147]. Gastrointestinal side effects and a serious case of febrile leukopoenia andthrombocytopenia after 10 days of resveratrol treatment were occurred [148].
Anthocyanin	No side effect [152].
Garlic	No side effect [159].
Berberine	Anorexia and upset stomach, diarrhea and constipation were the main adverse events [165].
Dihydromyricetin	No side effect [172].
Phyllanthus	Dyspepsia, diarrhea, per-rectal bleeding, chest pain, cough, headache, blurred vision, gum bleeding and flu-like symptoms [174].

berberine group. Muscle pain, fatigue, and cardiac symptoms were the main adverse events in subjects receiving pioglitazone [165].

In another study, 60 patients with type 2 diabetes and NAFLD were randomly assigned to receive either berberine or Xuezhikang for 12 weeks [166]. After intervention, B-ultrasound of liver was improved in both groups compare with baseline. Similarly, at the end of study in comparison to the baseline, other outcomes include ALT, AST, total cholesterol, TG, LDL-C, hemorrheology (including the whole blood viscosity, whole blood viscosity, high cutting reduction of whole blood viscosity, plasma cutting reductive low viscosity, blood sedimentation, RBC deposited, fibrinogen) were significantly reduced and HDL-C significantly increased in both groups. However, the differences between the study groups were not statistically significant [166].

3.21. Dihydromyricetin

Dihydromyricetin is a flavonoid which can be derived from *Ampelopsis grossedentata*, a medicinal and edible plant used in China for hundreds of years to treat common cold, sore throat, and icteric viral hepatitis [167]. The therapeutic properties of this herb are ascribed to its major biologically active compound dihydromyricetin, the most abundant flavonoid in *A. grossedentata* [167]. It has been suggested that dihydromyricetin may have several favorable effects on health including antioxidant, anti-inflammatory, hepatoprotective, anti-cancer, as well as lipid- and glucose-regulatory activities [168,169]. Several in vitro and in vivo studies have shown that *A. grossedentata* and dihydromyricetin improve serum lipid profile and enhance insulin sensitivity [170,171]. Therefore, dihydromyricetin could be useful in the treatment of NAFLD. In a randomized controlled trial, 60 adult NAFLD patients (confirmation by ultrasound) were assigned to receive either two 150 mg capsules of dihydromyrectin or placebo twice daily for three months [172]. Results of this study showed that in comparison to the placebo group, treatment with dihydromyricetin had no significant effect on severity of fatty infiltration assessed by ultrasound, as well as BMI, WC, blood pressure, serum ALP, TG, total cholesterol, HDL-C, and apolipoprotein A-I. However, serum ALT, AST, GGT, LDL-C, TNF-α, cytokeratin 18 and fibroblast growth factor 21were reduced and serum adiponectin was increased with dihydromyricetin treatment compared to placebo. No adverse effects were reported by the study subjects [172].

3.22. Phyllanthus

The plants of the genus *Phyllanthus* have been used as a medicinal herb for thousands of years in Asia in the treatment of diseases, including disturbances of the kidneys and urinary bladder, intestinal infections, diabetes, and hepatitis B virus [173]. One of the most important species in this genus is *Phyllanthus urinaria*, a plant which has been reported to displayhepatoprotective activities [174]. Indeed, it has been shown that *Phyllanthus urinaria*, like some other species of *Phyllanthus*, has a strong antioxidant capacity which contributes to its ability to suppress oxidative stress, lipid peroxidation and inflammation [173,175,176]. *Phyllanthus urinaria* has been shown to reduce hepatic steatosis and necroinflammation in vitro and in vivo [177]. To evaluate the effects of *P. urinaria* on NAFLD, a randomized controlled trial was conducted in 60 patients with histology-confirmed NASH [174]. In this study, patients were treated with either 1 g *P. urinaria* (two tablets) three times daily (n = 40) or receive a placebo (two tablets) three times daily (n = 20) for 24 weeks. After treatment, the NAFLD activity score, steatosis percentage, and steatosis grade assessed by biopsy were significantly reduced from baseline in the intervention group, while changes were not significant in the placebo group. However, there were no significant differences in the responses between *P. urinaria* and placebo groups. Furthermore, no notable changes were observed in lobular inflammation, portal inflammation and fibrosis in the study groups. Adverse events (e.g., dyspepsia, diarrhea, chest pain) were reported by approximately 30% of patients in both study groups. Severe adverse events (stroke, back pain) occurred in 5% of patients in both study groups. However, the number adverse events was not different between *P. urinaria* and placebo groups [174].

4. Conclusion

Although lifestyle modifications involving diet and exercise currently remain the first line of treatment for NAFLD, it appears that some herbal bioactive compounds could also potentially improve NAFLD treatment with an acceptable safety (Tables 1 and 2). At least

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Table 3
List of clinical trials evaluating the effects of nutraceuticals on non-alcoholic fatty liver diseases (retrieved from www.clinicaltrials.gov and www.irct.ir).

Nutraceutical	NCT identifier	Inclusion criteria	Method of assessment (sonography/fibroscan/biopsy)	Dose	Duration	Primary outcome	Phase
Silymarin	NCT02973295	Adults (both sexes) NAFLD patients Signed informed consent Possibility to follow instruction and the protocol	Fibroscan	2 × 200 mg 8 weeks (2 × 2 caps) Silymarin 2 × 100 mg 16 weeks (2 × 1 caps)	6-months	Change (Reduction) of parameters of liver steatosis defined by CAP (Controlled Attenuation Parameter) and liver fibrosis defined by LSM (liver stiffness measurements) during the 6 months period [Time Frame: 0 week (Initiation) and during 24–25 week (End of the Study)]	4
Silymarin	NCT02006498	Male or female 18 years of age or older. Diagnosed with NASH (refer to Section 5.2) AST and/or ALT greater than 40 IU/L. Must agree to adhere to alcohol consumption guideline. Weight gain//loss of no more than 10% between biopsy and screening or within 30 days of screening if the biopsy is performed during the screening period. No change in diabetic and/or lipid medications between biopsy and screening or within 30 days of screening if the biopsy is performed during the screening period	Biopsy	700 mg Capsules TID	12-month	To assess the efficacy of Silymarin as defined by an improvement in non-alcoholic steatosis (NAS) activity score by at least 30% from baseline compared to placebo [Time Frame: 12 months]	II (Completed)
Silymarin	NCT00389376	Males or females; age at least 18 years at screening Abnormal ALT >65 IU/L (ie, approximately 1.5 × upper limit of normal) Negative urine pregnancy test (for women of childbearing potential) documented within the 24-h period prior to the first dose of silymarin. Females of childbearing potential must be using two reliable forms of effective contraception during the study (while on drug and during follow-up) Hepatitis C virus (HCV) patients Previous treatment with any interferon-based therapy without sustained virological response. Serum HCV RNA above quantifiable level of detection by the assay, within 1 year of screening and after the end of therapy No antiviral therapy for at least 6 months prior to screening visit Nonalcoholic fatty liver disease (NAFLD) patients: Liver biopsy compatible with NAFLD within 3 years of screening Absence of other liver diseases by serological screening (anti-HCV, HBsAg), historical serological data from within 3 years of screening is acceptable. Before entering the study, subjects must agree not to consume alcohol for 48 h prior to PK sampling days or while on study.	Biopsy	Group 1: Placebo and 140 mg single dose + every 8 h Group 2: Placebo and 280 mg single dose Group 3: Placebo and 280 mg every 8 h Group 4; Placebo and 280 single dose + every 8 h Group 5: Placebo and 560 mg single dose + every 8 h Group 6: Placebo and 560 mg single dose + every 8 h ours Group 7: Placebo and 700 mg single dose + every 8 h	10 days	Adverse events [Time Frame: 10 days]	1

Table 3 (*Continued*)

Nutraceutical	NCT identifier	Inclusion criteria	Method of assessment (sonography/fibroscan/biopsy)	Dose	Duration	Primary outcome	Phase
Silymarin	NCT01511523	Male and female patients age 18 years and older. A clinical or histologic or radiographic diagnosis of NAFLD. Abnormities above normal range in hepatic function testing consisting of panels containing ALT, AST, AP, Total bilirubin and albumin. Negative urine pregnancy test (for females of childbearing potential) collected at screening followed by another negative serum pregnancy test collected within 24 h prior to the first dose of study drug. Female patients of childbearing potential must be on adequate birth control. Willingness to give written informed consent and willingness to participate in and comply with the study requirements.	NM	3 capsules administered BID once a day contain Vitamin E, Silymarin, and Carnitine.	30-weeks	Efficacy [Time Frame: 30 weeks], Normalization of hepatic AST, ALT, y-GT, albumin, alkaline phosphatase and total bilirubin.	unknown
Silymarin	NCT02369536	Adult subjectss with nonalcoholic fatty liver disease (NAFLD) presenting ultrasonographic abnormalities of steatosic liver (hyperechogenic parenchyma) with plasma levels greater than normal (ranges of each recruiting center) for at least one of the following parameters (aspartate aminotransferase AST, alanine aminotransferase ALT, γ – glutamyltranspeptidase γ-GT).	ultrasonography	Lifestyle counseling, administration of a nutraceutical mixture: fish oil 70% DHA (docosahexaenoic acid), phosphatidylcholine concentrated in sunflower oil, silymarin, choline bitartrate, curcumin, D-α-tocopherol; choline (82,5 mg, corresponding to 15% of the average intake of 550 mg per day in an adult man)	3-months	Change of hematic levels of hepatic enzymes [Time Frame: before and at the end of treatment (three months)] ALT, AST and/or γ-GT	recruiting participants
Silymarin	NCT00680407	Age at least 18 years at screening. Informed consent signature. AST (aspartate aminotransferase) or ALT (alanine aminotransferase) greater than 40 IU/L within one year of screening and at least once during the screening period. The participant must agree to adhere to the alcohol consumption guidelines. Have a liver biopsy performed within 12 months of randomization demonstrating features consistent with NASH without cirrhosis; NAS score of at least 4. Historical biopsy must include one Trichrome and one H&E slide, otherwise the biopsy must be redone. No change in diabetic medications or insulin sensitizers (if applicable) between biopsy and screening or during the screening period. Weight loss/gain of no more than 10% between biopsy and screening, or within 30 days of screening if the biopsy is performed during the screening period.	Biopsy	Group1: Silymarin 420 mg Group 2: Silymarin 700 mg	48–50 weeks	Efficacy – Improvement by at Least 2 Points in Histology (NAS) [Time Frame: 48–50 week treatment period]	2 (completed)

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Table 3 (*Continued*)

Nutraceutical	NCT identifier	Inclusion criteria	Method of assessment (sonography/fibroscan/biopsy)	Dose	Duration	Primary outcome	Phase
		Negative urine pregnancy test (for women of childbearing potential) documented within the 24-h period prior to the first dose of study medication. Females of childbearing potential must be using two reliable forms of effective contraception during the study (while on study drug and during follow-up).					
Green tea	NCT00977730	Age at entry at least 18 years. Serum alanine (ALT) aminotransferase activity that is above the upper limits of normal. Evidence of steatohepatitis on liver biopsy performed within the previous 6 months with a NAFLD activity score (NAS) of at least 3 (of a total possible score of 8) including a score of at least 1 each for steatosis, hepatocellular injury and parenchymal inflammation. Histological criteria of steatohepatitis include: (1) macrovesicular steatosis, (2) acinar zone 3 hepatocellular injury (ballooning degeneration), (3) parenchymal inflammation, and (4) portal inflammation. Additional (but not required) features include the presence of (5) Mallory's hyaline and (6) pericellular and/or sinusoidal fibrosis that predominantly involves zone 3. Written informed consent. Willingness to have a repeat percutaneous liver biopsy following 1 year of supplementation.	Biopsy	1 675 mg capsule Protandim PO/day; Protandim is a nutritional supplement composed of the following 5 botanical extracts: Bacopa Moniera extract, Milk Thistle extract, Ashwagandha powder, Green tea, and Turmeric extract	12-month	Change in NAS at study completion in the Protandim group compared to the placebo group. [Time Frame: 12 months]	completed
curcumin	NCT02908152	Adult patients diagnosed with type 2 diabetes based on ADA definition or who only take oral antidiabetic drug; CAP score >263.	Fibroscan	Curcumin 1500 mg, 1 capsule/day	12-weeks	Hepatic steatosis [Time Frame: [12 weeks]] measured by CAP score using Fibroscan	2, 3
Olive/canola oil	NCT02458586	Adult males who increased hepatic fat content (NAFLD) BMI between 30 and 35 kg/m^2	MR spectroscopy and ultrasound	Group1: Daily intake of 50 g of canola oil (rapeseed oil) Group2: Daily intake of 50 g of olive oil	8-weeks	Change in liver fat content [Time Frame: 4 and 8 weeks] change in liver fat content (MR spectroscopy and ultrasound) Change in hepatic insulin sensitivity [Time Frame: 8 weeks only], change in hepatic insulin sensitivity (euglycemic hepatic clamp)	
Soluble fiber	NCT02875392	Patients who are aged between 20–75 with NAFLD	Fibroscan	275 mg Oligo Fucoidan + 275 mg HS Fucoxanthin	6-month	improvement on AST [Time Frame: study period is up to 6 months] Assess the value of fatty liver and liver fibrosis with Fibroscan to check both AST& ALT	recruiting participants
Resveratrol	NCT01446276	Male 25–65 years Obesity (BMI >28 kg/m2, waist/hip ratio >0,95) Have nonalcoholic fatty liver disease (NAFLD)(intervention group) or do not have NAFLD (control group)	Biopsy	1.5 g resveratrol per day	6-month	Hepatic VLDL-TG secretion and peripheral VLDL-TG clearance [Time Frame: six month]- Changes from baseline after treatment with either resveratrol or placebo	has been completed

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Table 3 (*Continued*)

Nutraceutical	NCT identifier	Inclusion criteria	Method of assessment (sonography/fibroscan/biopsy)	Dose	Duration	Primary outcome	Phase
		May have hypertension and/or hypercholesterolemia Written informed consent					
Resveratrol	NCT02216552	13 to <18 years of age BMI considered overweight (BMI >25 kg/m2) or obese (BMI >30 kg/m2) Confirmed 1H-MRS defined hepatic steatosis (>5.5% fat/water) Parent/Guardian willing and able to provide written, signed informed consent, and subjects willing to co-sign parental consent Sexually active subjects must be willing to use an acceptable method of contraception Females of child bearing potential must have a negative pregnancy test at screening.	NM	Resveratrol Oral supplementation of resveratrol (ResVida) 75 mg twice daily (with breakfast and dinner) for a total daily dose of 150 mg for the duration of 30 days.	30-days	Safety/Adverse Event Outcome [Time Frame: Week 8] a. Primary Side effect profile determined by participant interview. Side effect profile determined by serum biochemistry: AST, ALT, total and conjugated bilirubin, Creatinine, sodium, potassium, calcium, magnesium, chloride and TC02, haemoglobin, haematocrit, white blood cell and platelet counts, erythrocytes, and fasting lipid levels (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides). Fasting glucose and insulin levels. PT/INR and PTT levels. b. Vital signs	Phase 2 Phase 3
Phyllanthus	NCT01680003	Male or non-pregnant females age 18 years or older Written informed consent obtained from patient or parents/guardian Elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels but less than 2.5times the upper limit of the normal range Patients with liver biopsy confirmed possible or definite steatohepatitis within the past 12 months prior to enrolment into the trial Possible steatohepatitis with activity score $\geq$3 OR definite steatohepatitis with activity score $\geq$5 A score of at least 1 for hepatocellular ballooning	Biopsy	Two capsules (250 mg $\times$ 2), three times daily, orally	48-weeks	Improvement in serum aspartate aminotransferase and alanine aminotransferase levels [Time Frame: 48 weeks]	Phase 2

Table 3 (*Continued*)

Nutraceutical	NCT identifier	Inclusion criteria	Method of assessment (sonography/fibroscan/biopsy)	Dose	Duration	Primary outcome	Phase
Silymarin	IRCT138805172308N1	Older than 20 years with nonalcoholic-fatty liver disease and liver enzymes >50 and proportion of ALT/AST >1 Excluding criteria: using drugs that affect liver tests during the last 2 months, viral hepatitis, hemochromatosis, autoimmune hepatitis, cirrhosis, diabetes mellitus, alcohol dependency, pregnancy, breast feeding, and infectious diseases	Sonography	Intervention group: 140 mg of Silymarin BID	6-months	ALT, AST, Sonographic markers	2–3
Silymarin	IRCT2016080614882N4	Obese or overweight child and adolescent with sonographic finding of fatty liver Exclusion criteria: Age less than 5 and more than 16 years old; patients with metabolic syndromes; viral hepatitis; wilson disease; auto immune hepatitis; juvenile hemochromatosis and other underlying diseases; allergy or intolerance to medication	Sonography	Livergol tablet containing silymarin(Goldaru Company, Iran) were administered with dosage of 5 mg per kg body weight divided in three dose with meal.	12 weeks	Grading of fatty liver in sonography	N/A
Silymarin	IRCT2015031721502N1	Age between 20–40 years old; patients who has white skin; patients who referred to the clinic for checkup; fatty liver is reported in sonography; agreement to be a part of the study; ALT level above 40. Exclusion criteria: patients that want to withdraw the study at any time; cirrhosis is reported in sonography; patients who are detected as Wilson, autoimmune hepatitis, viral hepatitis, alcoholic hepatitis, hemochromatosis; patients who are suffering from chronic liver disease; drug causes is to be considered for fatty liver; sensitive to drug; those who are affecting by drug side effects.	sonography	Nutri Liver Support 150 mg, oral, twice a day	2-months	ALT, AST	3
Green Tea	IRCT201404132365N8	Known case of NAFLD, diagnosed by ultrasound of the liver, liver biopsy or liver Fibroscan; age 18 years or older; willingness to participate in research. Lack of inclusion criteria: iron deficiency anemia (hemoglobin less than 12 for women and 13 for men); allergy to green tea; alcohol consumption more than 20 g daily; viral hepatitis B and C; autoimmune hepatitis; celiac; wilson; alpha-antitrypsin deficiency. Exclusion criteria: symptoms of allergy or adverse effects of green tea consumption; taking less than 80% of the delivered dose of green tea; pregnancy or lactation; unwillingness to continue the study.	Biopsy	green tea catechins (ECGC) 450 mg/d	3-months	Hemojuvelin gene expression	N/A
Green Tea	IRCT2013092611763N12	Adults (men & women)20–60 years with fatty live and Alanine Amino Transferase equal or higher than 40. exclusion criteria: kidney diseases, chronic lung disease, other hepatic disease, alcoholism.	NM	1 capsule of 500 milligrams Green Tea in a day	3-months	Lipid profile (LDL, Cholesterol, TG, HDL), ALT, AST	N/A

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Table 3 (*Continued*)

Nutraceutical	NCT identifier	Inclusion criteria	Method of assessment (sonography/fibroscan/biopsy)	Dose	Duration	Primary outcome	Phase
Flaxseed oil	IRCT2016011125957N1	Having NAFLD by medical diagnosis (using ultrasound); BMI = 25 and above; willingness to participate in the study, the absence of diabetes mellitus type 2;heart disease;cardiovascular and liver disease (cirrhosis, liver disease Alcohol, viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, biliary obstruction, liver damage induced by drugs hereditary Hemochromatosis, sclerosis cholangitis and antitrypsin deficiency of α-a-1);other serious diseases such as cancer;kidney failure and celiac disease, etc.);lack of pregnancy;lactation;lack of drugs that are causing fatty liver (methotrexate, tamoxifen, Valproate, etc.);avoiding the use of any type of lipid lowering agents (atorvastatin, lovastatin, pravastatin, etc.);fibrates (gemfibrozil, fenofibrate);lack of malnutrition;have no special diets such as vegan and vegetarian;not drinking alcohol and having over 18 years of age.	Ultrasound	20 g per day flaxseed oil	3-months	blood pressure, Lipid profile	N/A
Flaxseed oil	IRCT2013111715427N1	The enzyme Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) at least 1.5 times above the normal limit, confirmed by the kidney sonography; Meeting at least one of the following criteria: Within the age range of 15–60 years old, diabetes, Hyperlipidemia, and Obesity.	Sonography	Oral Flaxseed every day 3 times (1 g)	2-months	Liver Enzyme, blood glucose	2
Cinnamon	IRCT2015062922977N1	Consenting NAFLD patients 18–65 years old; evidence of fatty liver in ultrasonography with a score of 2 or more or alanine aminotransferase (ALT) levels up to 60 U/L	Ultra sound	Patients will receive 750 mg cinnamon capsules twice daily	12-weeks	Fatty liver score in ultrasound	1–2
Cinnamon	IRCT2015062115587N9	ALT level higher than 65U/L; Diagnosed fatty liver in ultrasonography; No alcohol and drug abuse; No history of chemotherapy in the past years; No history of other chronic liver diseases such as hepatitis B and hepatitis C, cirrhosis, bile diseases, autoimmune diseases, cancer and any genetic disorder that effects liver function such as Wilson's disease; No history of lipid-lowering drug use; No pregnancy and breast-feeding; No use of vitamin E supplements; No use of drugs that caused fatty liver, like tetracycline, vitamin A, methotrexate, amiodarone, tamoxifen, etc.; No history of use of hepatotoxic drugs in the last 6 months; No long-term use of herbal drugs	ultrasonography	Patients will receive 250 mg cinnamon capsules, 4 times a day	2-months	Reduction in ALT, AST serum level, Lipid profile	2–3

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Table 3 (*Continued*)

Nutraceutical	NCT identifier	Inclusion criteria	Method of assessment (sonography/fibroscan/biopsy)	Dose	Duration	Primary outcome	Phase
soy	IRCT201701162709N40	Patient aged 18–60 y; diagnosis of NAFLD in accordance to American Gastroenterological Association guidelines as follows: a) hepatic steatosis confirmed by ultrasonography, b) there are no cause for secondary steatosis such as alcohol consumption, hereditary disorders(e.g. hemochromatosis,wilson's disease),autoimmune diseaseses,hepatotoxic drugs (e.g. methotrexate, amiodaron, tamoxifen, corticosteroids, valproate and anti-viral drugs) and chronic hepatitis C; Absence of any other co-disorders including but not limited to other chronic liver diseases (hepatitis), cirrhosis, celiac, diabetes, thyroid disorders, breast cysts, as well as cardiovascular, renal, respiratory,inflammatory and autoimmune diseases; Absence of cancer or a history of cancer in patient and his/her first-degree relatives; BMI of 25–40 (kg/m2); having no allergy to soy milk; consuming no nutritional supplements during the last two months; Taking no anti-inflammatory drugs; hasn't any history of drug abuse and smoking; no pregnancy or lactation; willingness to participate and sign an informed written consent.	ultrasonography	One glass of soy milk (240 cc) is replaced with one serving of both starches and fats groups	8-weeks	Liver enzymes (ALT, AST, ALP, GGT), Lipid profile, and hepatic steatosis	N/A
Curcumin	IRCT2017012031423N1	1. having ALT and AST upper than highest normal level 2. have at least one of the following: A) Diabetes B) Hyperlipidemia C) Obesity 3. The age of 15–60	NM	80 mg curcumin, 2 times a day	2-month	BMI, liver enzymes, lipid profile	2–3
Curcumin	IRCT2014110511763N18	Not suffering from diseases such as cardiovascular problems; kidney; lung; thyroid disorders and liver problems such as hepatitis; chronic liver disease; nonalcoholic fatty liver disease; Pregnant and milking; BMW over 25; non-smoking and drugs such as celecoxib on inflammation	sonography	Capsules, 500 mg orally, once daily	2-months	Liver enzymes, lipid profile, hs-CRP	N/A

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Table 3 (*Continued*)

Nutraceutical	NCT identifier	Inclusion criteria	Method of assessment (sonography/fibroscan/biopsy)	Dose	Duration	Primary outcome	Phase
Curcumin	IRCT2015052322381N1	Age 15–60 years; rejection of causes that increase hepatic transaminases such as viral infections; autoimmune liver disease; poisons and toxins; Radiology approval of fatty liver.	Ultrasound	80 mg capsules· single dose per day	3-months	MCP-1, VEGF, – inflammatory cytokines and hs-CRP	
Olive oil	IRCT201111022709N20	Signing written informed consent, age between 20and 60, diagnosis of non-alcoholic fatty liver disease by fatty infiltration on ultrasound and abnormal serum liver function tests (AST or ALT >30 u/l in men and >20 in women), no smoking, BMI between 25–35, no pregnancy or lactation, no use of dietary supplements 2 month prior to enrollment, not having diabetes, acute heart disease, other form of liver disease (viral or autoimmune hepatitis, metabolic and hereditary liver disease), no usual use of Olive Oil in dietary pattern, no use of drugs that induces steatosis (amidarone, methotrexate, systemic glucocorticoid, tetracycline, tamoxifen, estrogen, anabolic steroids, valporic acid), no use of Lipid lowering drugs	Sonography	Extra Virgin Olive Oil, 20% of total daily energy requirement olive will be replaced with usual daily consumption of oil for every patient	12-weeks	Liver enzymes, steatosis severity	N/A
Olive oil	IRCT2016011825957N2	Having NAFLD by medical diagnosis (using ultrasound); BMI = 25 and above; willingness to participate in the study, the absence of diabetes mellitus type 2;heart disease; cardiovascular and liver disease (cirrhosis, liver disease Alcohol, viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, biliary obstruction, liver damage induced by drugs hereditary Hemochromatosis, sclerosis cholangitis and antitrypsin deficiency of α-a-1);other serious diseases such as cancer; kidney failure and celiac disease, etc); lack of pregnancy;lactation; lack of drugs that are causing fatty liver (methotrexate, tamoxifen, Valproate, etc.); avoiding the use of any type of lipid lowering agents (atorvastatin, lovastatin, pravastatin, etc.); fibrates (gemfibrozil, fenofibrate); lack of malnutrition; have no special diets such as vegan and vegetarian; not drinking alcohol and having over 18 years of age	Ultrasound	20 g olive oil per day	3-months	Insulin resistance index, TNF-Alpha, Oxidative stress index	N/A

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some degree of amelioration was found in liver functional tests, including liver enzymes, metabolic and biochemical parameters (e.g., blood lipids, glucose and insulin), inflammatory biomarkers (e.g Il-6 and TNF-α), and diagnostic methods for NAFLD (e.g., liver ultrasonography). These herbal medicines seem to have a greater role in inhibiting oxidative stress by reducing insulin resistance and fat accumulation in the liver, and interacting with liver metabolism of lipids.

Since NAFLD is a complex disease that involves several organs and tissues, it is preferable to use combined therapy including therapeutic agents (eg, bioactive compounds) along with lifestyle interventions or other non-pharmacological therapies such as behavioral therapies. Those patients who do not reach the targets with the only classical therapy are candidates of receiving herbal nutraceuticals in order to benefit from additive effects of these agents. However, it should be considered that nutraceuticals are marketed as mixtures of different compounds, so their prescription is not always easy for the physician, as the preparation to be administered, the content of the individual ingredients and the dosages must be adequate, and it is also necessary to evaluate the cost, long-term effects and potential risk of drug interactions for patients. When purified phytochemicals (e.g. curcumin and berberine) are used, the aforementioned concerns are considerably addressed compared with herbal extracts.

While several clinical trials are underway to assess the therapeutic effects of additional nutraceuticals and plant-based products (Table 3), it is suggested that scientists focus more on assessing the efficacy of plant-derived therapeutic agents in the future through conducting larger randomized clinical trials of longer duration and using gold standard diagnostic strategies to precisely determine the role of herbal medicines in the treatment of NAFLD.

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MB, VN and CNB Designed research; MB an CNB conducted research; CNB and VN analyzed data; MB and CNB wrote paper; AS had primary responsibility for final content; AS is the sole author had responsibility for all parts of the manuscript; All authors read and approved the final manuscript.

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