DERLEME REVIEW

DOI:10.5336/pharmsci.2022-91392

Herbal Preparations Used Against Fatty Liver Disease: Systematic Review

Karaciğer Yağlanmasına Karşı Kullanılan Bitkisel Preparatlar: Sistematik Derleme

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ABSTRACT The fatty liver disease is defined as more than 5% of liver histiocytes filled with fatty vacuoles, depending on diet and independent of alcohol consumption. As it is known, fatty liver and related disorders are common, but still have no effective treatment. It is one of the important health problems in developed countries, associated with social and economic problems. Non-alcoholic fatty liver disease (NAFLD) is among the most common chronic metabolic disorders. It was observed that the prevalence of NAFLD has increased significantly worldwide in recent years. With advancing obesity epidemics, NAFLD has become the most common cause of chronic liver disease both in adults and children. Therefore, the clinical and economic burden of the disease is remarkable and increasing within the health system. While fatty liver is a metabolic disorder that has no definite drug treatment today, there are some traditional preparations used for this purpose as ethnobotanically. According to ethnobotanical studies in the current literature associated to liver diseases; various in vitro, in vivo, or clinical experimental studies were reported with successful results. Thus, in this present review, studies on natural sourced raw materials, herbal formulations related to liver diseases, especially fatty liver, obesity, hyperlipidemia were compiled mainly from ethnobotanical origin.

Keywords: Fatty liver; extract; herbal drug; natural product

ÖZET Beslenmeye bağlı, alkol tüketiminden bağımsız karaciğer histiositlerinin %5'ten fazlasının yağ vakuolleriyle dolu olması "yağlı karaciğer hastalığı" olarak tanımlanmaktadır. Bilindiği üzere karaciğer yağlanması ve karaciğer yağlanmasına bağlı rahatsızlıklar sık görülen ancak günümüzde kanıtlanmış etkin bir tedavisi olmayan metabolik rahatsızlıklardır. Ülkemizde de önemli sağlık sorunlarının başında gelmekte olup, sosyal ve ekonomik problemleri beraberinde getirmektedir. Nonalkolik yağlı karaciğer hastalığı, gelişmiş ülkelerde en yaygın kronik metabolik rahatsızlıklar arasındadır. Son yıllarda alkole bağlı olmayan yağlı karaciğer hastalığı prevalansının dünya genelinde önemli bir şekilde arttığı gözlenmiştir. İlerleyen obezite salgınları ile nonalkolik yağlı karaciğer hastalığı, erişkinlerde ve çocuklarda kronik karaciğer hastalığının en yaygın nedeni hâline gelmiştir. Bu nedenle yağlı karaciğer hastalığının klinik ve ekonomik yükü dikkate değerdir. Karaciğer yağlanması, günümüzde kesin bir ilaç tedavisi olmayan bir metabolik rahatsızlık iken, halk arasında bu amaçla kullanılan bazı geleneksel preparatlar mevcuttur. Karaciğer rahatsızlıklarında bitkiler etnobotanik çalışmalarda yer almış; çeşitli in vitro, in vivo veya klinik deneysel araştırmalarda yer almış olup, başarılı sonuçlar alınmıştır. Bu derlemede, bilhassa karaciğer yağlanması, obezite, hiperlipidemi başta olmak üzere karaciğer rahatsızlıkları ile ilişkili bitkiler, bitkisel formülasyonlar ve bitkilerden elde edilen doğal kaynaklı ham maddeler ile yapılan çalışmalar listelenmiştir. Gerek halk arasında kullanımları içeren, gerek deneysel çalışmaları (in vivo ve klinik çalışmalar) içeren makaleler derlenmiş ve özetlenmiştir.

Anahtar Kelimeler: Karaciğer yağlanması; ekstre; bitkisel ilaç; doğal ürün

The liver helps to regulate the body's energy metabolism and eliminate toxins, as it is well known. In addition, the liver plays vital role in the digestive system and process. It converts vital micronutrients into usable metabolites for the biological systems and performs many functions.[1]

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Peer review under responsibility of Journal of Literature Pharmacy Sciences.

Received: 18 May 2022 ***Received in revised form:*** 31 Aug 2022 ***Accepted:*** 08 Nov 2022 ***Available online:*** 16 Nov 2022

Liver diseases can be evaluated within a wide range of disorders that damage a liver tissue or its function. Liver tissue becomes inflamed mainly through contact with toxins or viruses. Various liver disorders are known, where the most common liver diseases are liver cirrhosis, hepatitis, fatty liver, and bile duct obstruction. Hepatitis is very common all over the world and it is also seen quite frequently in Türkiye. Cirrhosis is a chronic liver disease that causes deterioration of the natural structure of the liver. Fatty liver is another common liver condition connected with obesity. It is a liver disease that usually develops due to improper eating habits and physical inactivity. Fatty liver is on its way to becoming the most common liver disease with increasing obesity. Especially non-alcoholic fatty liver disease (NAFLD) is a disease whose incidence is increasing, while the age of its incidence is gradually decreasing in Türkiye.[2-4] In addition, NAFLD develops due to drug use. Especially drugs that are metabolized in the liver have such an effect. Plants used in traditional medicine and used in ethnobotany against fatty liver are also promising.[5]

In this present review, traditional usages, and experimental studies for drug discovery from herbal sources were investigated in the treatment of NAFLD. The pharmacological and pharmacokinetic results of the studies were evaluated and reflected in this present literature review. In addition, the results of both experimental and clinical studies of secondary metabolites obtained from plants were investigated separately and the details were shared in the section of the plant from which they were obtained.

Natural resources are frequently used in the treatment of liver diseases as well as in the treatment of many diseases. There are successful results obtained with various in vitro methods, in vivo experiments, and clinical studies (Table 1). In the studies, sometimes the whole plant, sometimes the plant extract or formulations containing a component of natural origin, or the effect of the natural component directly were examined. In this section, all of them will be discussed separately. In this study, the results of the plants used ethnobotanically against fatty liver and the experimental studies of these plants are given, and these results are summarized in a table. The information given in the section below is given in alphabetical order of plant names.

PLANT EXTRACTS AND THEIR BIOACTIVE METABOLITES

***Agrimonia eupatoria* L.:** It was reported that a decoction prepared from the aerial part of the plant is used against liver diseases ethnobotanically in Iran. In addition, in previous studies, different extracts were investigated against fatty liver in cell culture.[6,7] In this study, it was determined that the ethyl acetate extract *A. euparotia* suppressed triglyceride (TG) accumulation. Also, it inhibited the expression of peroxisome proliferator activated receptor-γ (PPAR-γ) in liver. Although all the results in the study are in vitro data, the results obtained showed that ethyl acetate fraction has better results than ethanol, methanol, and water extracts.

***Allium L.* sp.:** *A. tripedale* is a garlic species used as an ethnobotanical are consumed raw and due to its antihyperlipidemic effect.[8] Another *Allium* species, *A. sativum*, which is also used in food, bulbs were also tested against NAFLD model in mice. It was shown to decrease alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Also, high antioxidant parameters such as glutathione peroxidase and superoxide dismutase activities were observed with the *A. sativum* bulb extract.[9] In addition, in a clinical study with the dry powder of *A. sativum* bulbs, it was found to be quite effective against fatty liver. In this previous study, a decrease in body mass was observed in the garlic powder group.[10] Another *Allium* species, aqueous extract of *A. saralicum* R.M. Fritsch extract was investigated on high-fat diet (HFD)-induced NAFLD in Wistar albino rats. *A. saralicum* significantly reduced liver enzymes and cholesterol, TG, and glucose levels. Moreover, the *A. saralicum* extract reduced the degree of hepatic steatosis.[11]

***Alisma orientale* (Sam.) Juz.:** *A. orientalie* methanolic extract was studied on experimental NAFLD. Extract administration significantly reduced liver and serum lipids; high level of serum glucose was lowered, and insulin resistance was improved. *A. orientale* also helped in preventing oxidative stress

TABLE 1: Ethnobotanical usages and experimental studies of plant materials against fatty liver disease.

Plant	Activity and ethnobotanical studies	Extraction solvent/used parts	References
Agrimonia eupatoria L.	Ethnobotanical In vitro: Suppressed TG accumulation and inhibited the expression of lipid marker gene	Ethyl acetate/aerial parts	6,7
Allium tripedale Trautv.	Ethnobotanical	As food and brewed/aerial parts	8
Allium sativum L.	In vivo: To decrease AST, ALT levels, and high SOD, GSH-Px activities Clinical studies: Weight lose	Water/bulbs	9,10
Allium saralicum	In vivo: Reduced the degree of hepatic steatosis	Distilled water/leaves	11
Alisma orientale (Sam.) Juz.	In vivo: Reduced serum and liver lipids; high level of fasting serum glucose was lowered and insulin resistance	Methanol/rhizomes	12
Berberis vulgaris L.	In vivo: Hepatic mRNA and lncRNA expression Clinical studies (berberine): Effective against fatty liver	Hydro alcohol/roots	13-15
Betula sp.	In vivo (betulinic acid): SREBP-1 activity is effective against fatty liver by inhibiting via the AMPK-mTOR-SREBP signalling pathways	Not extraction	16
Camellia sinensis L. (Kuntze)	In vivo (epigallocatechin gallate): Adiposity and inflammation were reduced, and ALT, insulin, TG and glucose levels decreased. Clinical study: ALT levels showed significant decreases	Green tea extract supplement (not extract)/leaves	17,18
Capparis spinosa L.	Clinical study: ALT, LDL, and TG were significantly decreased	Cool-boiled water/fruits	19
Carica papaya L.	Ethnobotanical	As food/fruits	20
Cassia obtusifolia (L). H. S. Irwin & Barneby	Ethnobotanical In vivo: Hyperlipidemia for NAFLD rats, prevents reduction of LDL-R mRNA expression	Ethanol/seeds	21-23
Chrysanthemum morifolium Ramat.	In vivo: Lower serum TC levels and liver weight in rats	75% ethanol/flowers	24
Cichorium intybus L.	Ethnobotanical In vitro: Downregulation of SREBP-1c and PPAR-α genes following steatosis induction	Ethanol/seeds	8,25-28
Cinnamomum sp.	Clinical studies: Patients with NAFLD were HOMA index, blood sugar, TC, TG, ALT, GGT and AST decreased significantly	Capsules of cinnamon (not extract)	29
Citrus sp.	Ethnobotanical In vivo: Decreased serum lipid index, decreased expression of proinflammatory cytokines and preventing liver histopathology	Ethanol/peel	20-30
Crataegus aronia (L.) Bosc ex DC.	In vitro: Decreased the liver index, increased HDL-cholesterol, and decreased LDL-cholesterol in the blood	Distilled water/fruits	31
C. pinnatifida	In vitro: Against fatty liver via the adiponectin/AMPK pathway	Water/leaves	32
Crocus sativus L.	In vivo (saffron and crocin): Low levels of hepatic marker enzymes, including AST, ALT, ALP and albumin Clinical studies (crocin): Improved liver enzymes.	Ethanol/stigma of flowers	33,34
Cornus mas L.	Clinical studies: Reduced serum ALT, AST, cytokeratin 18 levels	Hydro ethanol/fruit	35

TABLE 1: Ethnobotanical usages and experimental studies of plant materials against fatty liver disease *(devamı)*.

Plant	Activity and ethnobotanical studies	Extraction solvent/used parts	References
Curcuma longa L.	In vivo (curcumin): Effective against fatty liver by inhibiting nuclear factor kappa B activation. Reduced inflammation significantly Clinical studies (curcumin): Against fatty liver disease	Supplemented diet with curcumin (not extract)	36,37
Cynara scolymus L.	Ethnobotanical Clinical studies: Decreasing ALT, AST levels	Boiling water/leaves	38
Dioscorea bulbifera L.	In vivo: Exhibited potential damage to liver function	Ethanol/rhizomes	39
D. nipponica	In vivo: Trillin was against fatty liver and effected antihyperlipidemic Diosgenin is effective in fatty liver Dioscin prevent NAFDL	Ethanol/rhizomes-roots	40,41
Glycine max L.	In vivo: Hepatic PPAR-γ, TNF-α and malondialdehyde levels increased	Dissolved in DMSO	42
Lactuca sativa L.	Ethnobotanical In vivo: Improves serum lipid levels, prevents lipid peroxidation, and increases the antioxidant system	Dietary supplementation/red-pigmented leaf	8-43
Malva neglecta L.	Ethnobotanical	As food and brewed/leaves and roots	8
Melissa officinalis L.	Clinical studies: Significant decrease in serum level of AST, ALT, BMI and fatty liver grade	Boiled water/leaves	44
Morus alba L.	In vivo: Liver X receptor-α-mediated lipogenesis and hepatic fibrosis markers improved such as α-smooth muscle actin. Regulating hepatic fibrosis, lipid metabolism and antioxidant defence system	Hydro ethanol/leaves	45-47
Myristica fragrans	In vivo: Decrease the expression of lipid synthesis related genes FASN and SREBP-1c and lower the lipid content	70% ethanol/seeds	48
Nigella sativa L.	Clinical studies: Significant improvement in both body weight and impaired liver enzymes	Boiled water/seeds	44
Olea europea L.	Ethnobotanical In vivo: Significantly decreased TG and LDL levels, while significantly increased HDL levels Clinical trials: Reduction in weight and BMI	Organic solvent extraction/leaves and fruits	8,49-51
Panax ginseng C.A.Mey.	In vivo: Activation of AMP-activated protein kinase and reduced hepatic fat deposition.	Organic solvent extraction/roots	52
Pistacia chinensis Bunge	Ethnobotanical In vivo: Decreased serum-liver enzymes such as AST, ALT, and ALP	Methanol/fruits	53
Pluchea indica (L.) Less.	Ethnobotanical In vivo: Improvement of hyperglycemia, dyslipidemia with TC, LDL-cholesterol, HDL-cholesterol, and TG and obesity	Distilled water/aerial parts	21,54
Punica granatum L.	In vivo: Reducing hepatic enzymes, cholesterol, TGs, and LDL	Ethanol/peels	55
Rhododendron oldhamii Maxim.	In vitro: Inhibiting the free fatty acid-induced accumulation of fat In vivo: C57BL/6 mice, reduced TC and TG	Ethyl acetate/leaves	56
Rhus cinensis Mill.	In vivo: Regulating several key proteins involved in lipid metabolism, inflammation, and apoptosis of hepatocytes, namely by increasing p-AMPK expression levels	Ethanol/fruits	57
Rosa damascena L.	In vivo: Increase in TC, TG, LDL plasma lipid levels and reduced HDL levels	70% ethanol/flowers	58
Silybum marianum (L.) Gaertn.	In vitro: Inhibiting hepatic stellate cell activation In vivo: Improved lipid profile and hepatic enzyme activity Clinical studies: Normalisation of transaminase, decreased of GGT significantly	Hydro alcohol/seeds	26,36,59

TABLE 1: Ethnobotanical usages and experimental studies of plant materials against fatty liver disease *(devamı)*.

Plant	Activity and ethnobotanical studies	Extraction solvent/used parts	References
Taraxacum officinale (L.) Weber ex F.H.Wigg	Ethnobotanical In vivo: Suppressed liver lipid accumulation, reduced insulin resistance and lipid in C57BL/6 mice fed HFD via the AMPK pathway	Water/leaves	21-62
Triticum aestivum L.	In vivo: Reduced body weights, serum TC, and LDL cholesterol levels in HFD-fed mice and decreased in expression of PPAR-γ and FASN	Aqueous-ethanol/sprouts	63-66
Urtica dioica L.	Ethnobotanical In vivo: Decreased blood lipid levels	70% ethanol/leaves	8,67
Vaccinium vitis-idea L.	In vivo: Protect against liver injury, in part by attenuating hepatic lipid accumulation, oxidative stress, and inflammatory response	Dietary supplementation	68
Vernonia amygdalina Delile	Ethnobotanical	As food/leaves	20
Vitis vinifera L.	Ethnobotanical In vivo: Plasma leptin level was significantly lower, plasma adiponectin level was higher Clinical studies (resveratrol): Antihyperlipidemic activity and improving NAFLD-related parameters	Dietary supplementation/grape skin and seeds	8,21,36,69
Zingiber officinale L.	In vivo (ginger): Activating the peroxisome proliferator-activated receptor, induces adiponectin and down-regulated proinflammatory cytokines	Dietary supplementation/rhizomes	70

TG: Triglyceride; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; SOD: Superoxide dismutase; GSH-Px: Glutathione peroxidase; SREBP-1: Sterol receptor element-binding protein 1c; AMPK: Adenosine-monophosphate activated-protein kinase; mTOR: Mammalian target of rapamycin; LDL: Low-density lipoprotein; NAFLD: Non-alcoholic fatty liver disease; TC: Total cholesterol; PPAR-γ: Peroxisome proliferator activated receptor-γ; HOMA: Homeostatic model assessment; GGT: Gamma-glutamyl transferase; HDL: High-density lipoprotein; ALP: Alkaline phosphatase; TNF-α: Tumor necrosis factor-α; DMSO: Dimethyl sulfoxide; BMI: Body mass index; FASN: Fatty acid synthase; HFD: High-fat diet.

by activating antioxidant enzymes and reducing lipid peroxidation. In the treated rats, aminotransferase abnormalities, liver injury, and markers of hepatomegaly were improved.[12]

***Berberis vulgaris* L.:** The antihyperlipidemic and anti-fatigue effects of the hydro alcoholic extracts obtained from its roots were observed.[13] In addition, berberine, the known secondary metabolite of *Berberis* species, was found to be effective against fatty liver in clinical studies. In addition, in animal studies, berberine was investigated for hepatic gene expression profiles in NAFLD models. Berberine was demonstrated to have an effect in modulating hepatic gene expression profiles of a large set of genes in fatty liver. Among the genes regulated by berberine, numerous important genes associated with functions related to liver metabolism and NAFLD were identified.[14,15]

***Betula* sp.:** Betulinic acid is a secondary metabolite found to be very effective against fatty liver in many studies. Sterol receptor element-binding protein 1c (SREBP-1) activity is effective against fatty liver by inhibiting different pathways.[16]

***Camellia sinensis* L. (Kuntze):** Experimental studies showed that *C. sinensis* influences fatty liver disease. In this clinical study, significant decreases in liver parameters were observed after 12 weeks in the treatment group. ALT levels showed significant decreases in both placebo and treatment groups.[17] Epigallocatechin gallate, which is the most abundant catechin in tea, was found to be very effective against fatty liver in animal experiments. Compared to the control group, adiposity, ballooning degeneration, inflammation, and necrosis were significantly increased in the HFD group. In epigallocatechin gallate group, adiposity and inflammation were reduced compared to the HFD group, and there was a decrease in ALT, insulin, TG and glucose levels compared to the fatty diet group.[18]

***Capparis spinosa* L.:** Eating its fruits were studied in patients with NAFLD in experimental clinical studies and were found to prevent fatty liver. After 12 weeks, a reduction in weight and waist circumference was observed in patients treated with *C. spinosa* berries. It was determined that ALT, low-density lipoprotein (LDL), and TG were significantly decreased in the extract group.[19]

***Carica papaya* L.:** In traditional medicine, its fruits are known for their fat-burning effect.[20]

***Cassia obtusifolia* (L).H.S. Irwin & Barneby:** It is known that the seeds are used against fatty liver traditionally.[21] In addition, different extracts of the seeds were experimentally found to be successful in the treatment of NAFLD and hyperlipidaemia. In the group given *Cassia* extract in rats, it significantly reduced high biomarkers in NAFLD. *Cassia* treatment also prevents reduction of LDL-R mRNA expression and improves histopathological changes.[21-23]

***Chrysanthemum morifolium* Ramat.:** After *C. morifolium* treatment, serum total cholesterol (TC) levels and liver weight decreased in rats, but no decrease in serum triacylglycerol levels was observed.[24]

***Cichorium intybus* L:** Its roots are used ethnobotanically in the treatment of hyperlipidaemia.[8,25] In previous studies, its effect on NAFLD was demonstrated in vivo.[26,27] The activity of *C. intybus* seed ethanolic extract on hepatic steatosis induced by diabetes mellitus and bovine serum albumin-oleic acid complex in HepG2 cells was evaluated. The expression levels of SREBP-1c and PPAR-α were determined. Histological damage to cells and tissues (steatosis-inflammation-fibrosis) and downregulation of SREBP-1c and PPAR-α genes following steatosis induction were prevented by dandelion extract in concomitant treatment. Dandelion had a greater stimulatory effect on PPAR-α, acted as a PPAR-α agonist. Its seeds were also studied in another detailed NAFLD model and it was shown to be effective from different pathways.[28]

***Cinnamomum* sp:** The effect of cinnamon against diabetes is widely known. In addition, it is recorded in the literature that it can be used against hyperlipidaemia and fatty liver, together with the deterioration of liver metabolism and its effect against hepatotoxicity. In a clinical study, patients with NAFLD were randomized to receive cinnamon capsules. In the treatment group, homeostatic model assessment (HOMA) index, blood sugar, TC, TG, ALT, gamma-glutamyl transferase, and AST decreased significantly.[29]

***Citrus medica* L. and *Citrus aurantifolia* (Christm.) Swingle:** Both types of *Citrus* are used ethnobotanically in Nigeria against obesity.[20] In addition, *C. aurantifolia* peel ethanolic extracts were investigated in terms of their effects on fatty liver in mice. The results show that *Citrus* extract significantly reduces HFD-induced NAFLD, as indicated by the decreased serum lipid index and preventing liver histopathology. It also showed decreased expression of proinflammatory cytokines compared to untreated mice. These results showed that *Citrus* peel extract prevented HFD-induced NAFLD by reducing plasma TG and cholesterol levels and lipid synthesis.[30]

***Crataegus aronia* (L.) Bosc ex DC. and *Crataegus pinnatifida* Bunge:** *C. aronia* fruits were shown to have a potential protective effect against NAFLD. In previous studies, *C. aronia* decreased the liver index, increased high-density lipoprotein (HDL)-C, and decreased LDL-C in serum samples. *C. aronia* also significantly improved oxidative stress biomarkers and liver enzymes that indicate liver damage.[31] The water extract of *C. pinnatifida* leaves was found to be effective against fatty liver via the adiponectin/adenosine-monophosphate (AMP) activated-protein kinase (AMPK) pathway.[32]

***Crocus sativus* L.:** The activity of saffron ethanol extract and crocin in NAFLD of HFD-induced rats was investigated. A decrease in the levels of AST, alkaline phosphatase, ALT, and albumin, was observed in the groups given saffron and crocin.[33] In addition, in a clinical study, it was revealed that while the liver enzymes of the crocin-containing group improved, the liver enzyme results of the extract group were not significant.[34]

***Cornus mas* L.:** The activity of *C. mas* fruit hydro ethanolic extract on liver function in NAFLD was investigated in clinical trials. Serum ALT, cytokeratin 18 (CK-18) levels, AST, steatosis and fi-

brosis scores were analysed. After 12 weeks, *C. mas* fruit extract was reduced serum ALT, AST, and CK-18 levels.[35]

***Curcuma longa* L.:** Curcumin, the major metabolite of turmeric, is also a popular secondary metabolite subject to biological activity studies. Clinical trials were often conducted with curcumin in efficacy studies against fatty liver disease.[36] Curcumin was found to be effective against fatty liver in mice by inhibiting nuclear factor kappa B activation. Curcumin significantly reduced inflammation from fatty liver but had no effect on steatosis or hepatic lipid peroxide level.[37]

***Cynara scolymus* L.:** Different artichoke preparations are used both in traditional medicine and in pharmaceutical forms against liver ailments. There are also experimental clinical studies supporting that artichoke is especially effective against fatty liver. The results showed that the liver enzymes of the patients after using the *C. scolymus* for ALT and AST enzymes were increased.[38]

***Dioscorea bulbifera* L.:** Ethanol extracts and aqueous fractions of *D. bulbifera* exhibited potential damage to liver. The degree of *D. bulbifera* toxicity correlates with the concentration and duration of extract administration.[39] Trillin, a saponin obtained from the roots of another *D.* species, *D. nipponica*, was also investigated against fatty liver and its anti-hyperlipidemic effect was observed.[40] Diosgenin, another saponin component obtained from the plant, is a very effective compound in fatty liver. Dioscin was shown to prevent NAFLD in HFD-induced mice.[41]

***Glycine max* L.:** Genistein, an isoflavone compound in soybean, was found to be effective in fatty liver by increasing Hepatic PPAR-γ. The findings were that hepatic tumor necrosis factor-α (TNF-α) and malondialdehyde levels were increased in the NAFLD group.[42]

***Lactuca sativa* L.:** This plant, which is a vegetable known as lettuce, is indispensable for weight loss diets. Its leaves are ethnobotanically used as a fat reducer.[8] The red leaf one was found to prevent obesity in HFDs. Mice fed the lettuce diet had a 46% lower atherosclerotic index compared to the control diet. Antioxidant content increased significantly with lettuce supplementation. This study showed that supplementing a HFD with 8% red-pigmented leaf lettuce improves serum lipid levels, prevents lipid peroxidation, and increases the antioxidant system.[43]

***Malva* sp.:** The species of this plant, known as mallow, is widely grown all over the world and is used for various purposes. One of these species, *M. neglecta*, is popularly used against obesity as ethnobotanically.[8]

***Melissa officinalis* L.:** Lemon balm was tried in fatty liver studies in combination with black cumin and successful results were obtained in clinical studies. A decrease in serum level of AST, ALT, body mass index (BMI) and fatty liver grade was observed in clinical trials. It showed a reduction in the degree of fatty liver in the treatment group. *M. officinalis* preparations based on traditional Iranian medicine can reduce body weight and liver enzymes and improve the degree of fatty liver in NAFLD.[44]

***Morus alba* L.:** *M. alba*, which is a food consumption, is known for its liver-protecting properties.[21] There are also studies supporting this situation. It was shown to be effective against various liver disorders. Successful results were obtained especially against fatty liver disease for its leaves and fruits both. *Morus* extract has beneficial effects on NAFLD by regulating hepatic fibrosis, lipid metabolism, and antioxidant defence system.[45-47]

***Myristica fragrans* Houtt.:** In vivo results showed that *Myristica* ethanol extract inhibited the expression of free fatty acids (FFAs)-mediated inflammation-associated cytokines interleukin-6 and TNF-α in cells.[48]

***Nigella sativa* L.:** Black cumin is a widely used herb for both food and therapeutic purposes. Its effects against fatty liver were also investigated in an experimental clinical study. In human experiments, it was noted that there was an improvement in both body weight and impaired liver enzymes in the group given *N. sativa* seeds.[44]

***Olea europea* L.:** Olives and olive oil are included in diets due to their cholesterol-lowering effect. It is also included in ethnobotanical studies in this way.[8] There are many NAFLD studies conducted with both the leaves and fruits of the plant. Body

weight was significantly reduced in mice given olive extract. The olive oil group decreased TG and LDL levels. Olive oil lowers serum TGs, normalizes liver enzymes and reduces fat accumulation in the liver.[49,50] Another study conducted with olive oil measured the rates of fatty liver in patients fed with olive oil. The olive oil group had a reduction in weight and BMI.[51]

***Panax ginseng* C.A.Mey.:** A combination prepared with ginseng and garlic was shown to be successful in NAFLD in experimental studies. In addition to ginseng extract, its bioactive component, ginsenoside, was also investigated against fatty liver and it was found to be effective in fatty liver through activation of AMP-activated protein kinase. After chronic intraperitoneal administration, ginsenoside significantly reduced hepatic fat deposition in obese rats induced by an HFD.[52]

***Pistacia chinensis* Bunge:** The fruits of this species are traditionally used in liver diseases and were found to be effective in fatty liver experimentally.[53]

***Pluchea indica* (L.) Less.:** It is known that it is used to protect liver health in traditional medicine.[21] Studies on obesity were done in rats and significant results were obtained with this plant. The effect of *P. indica* tea on the improvement of hyperglycemia; dyslipidemia with TC, LDL, HDL, and TG; and obesity in mice on an HFD. Furthermore, histological analysis indicated that the mean area and amount of perigonadal fat adipocytes of the extract-treated groups were lower and higher than the HFD group, respectively.[54]

***Punica granatum* L.:** The effects of different extracts obtained from pomegranate against fatty liver were investigated in rats and successful results were obtained. The HFD group showed increases in hepatic enzymes, cholesterol, TGs, and LDL compared to the other groups. Histopathological examination results showed Grade 4 fatty liver changes in the HFD, Grade 1 in the extract group.[55]

***Rhododendron oldhamii* Maxim.:** The mechanism of preventing NAFLD in mice was investigated by extracts obtained from the leaves of the plant. The ethyl acetate fraction exhibited a potent oil deposition inhibitory activity. In addition, the ethyl acetate fraction of *R. oldhamii* leaf ameliorated NAFLD syndrome and reduced TC and TG in HFD-induced mice.[56]

***Rhus chinensis* Mill.:** The preventive effect and underlying mechanisms of extracts from *R. chinensis* fruits against NAFLD were elucidated. The results showed that it significantly improved some critical biochemical indices including all liver and antioxidant enzymes. Furthermore, immunohistochemistry and western blot analyses revealed that it can ameliorate NAFLD by regulating several key proteins involved in lipid metabolism, inflammation, and apoptosis of hepatocytes, namely by increasing p-AMPK expression levels.[57]

***Rosa damascena* L.:** The beneficial effect of *R. damascena* extract on an animal model of NAFLD was investigated. *R. damascena* reduced body weight, liver fat accumulation, TG, TC, LDL levels, and elevation of liver enzymes. In conclusion, the *R. damascena* dietary supplement has a therapeutic effect in NAFLD.[58]

***Silybum marianum* (L.) Gaertn.:** Its effects against fatty liver were proven in many experimental studies.[26,59]

In addition to its extract, there is a lot of scientific evidence on the effect of silybin and silymarin against fatty liver.[36]

***Taraxacum officinale* (L.) Weber ex F.H. Wigg:** The aerial parts of the plant are a very valuable therapeutic agent for many liver diseases.[21] Its effects and mechanisms of action against liver damage and fatty liver were investigated in animal experiments. The treated HFD significantly reduced hepatic lipid accumulation. Body and liver mass of the treatment groups were lower than that of the patient group, and supplementation of the extract significantly suppressed TG, TC, insulin, serum glucose level, and HOMA Insulin Resistance. *Taraxacum* significantly suppressed liver lipid accumulation, reduced insulin resistance and lipid in C57BL/6 mice fed HFD via the AMPK pathway.[60-62]

***Triticum aestivum* L.:** The use of wheat, which is the main ingredient of bread, for weight loss and against fatty liver was recorded.[63] In addition, many studies showed its antiobesity, fatty liver and lipid-lowering effects. The activity of *T. aestivum* aqueous-

ethanol extract in obese mice were investigated. The extract significantly reduced body weights, serum TC, and LDL levels in HFD mice. In the treatment group, lipid accumulation in epididymal white adipose tissue (EWAT) and liver was decreased, and TC and lipid levels were decreased. With the extract treatment, serum leptin and adiponectin concentrations were decreased and showed decreases in the expression of PPAR-γ and fatty acid synthase in EWAT. Moreover, the administration of the extract increased PPAR-α protein levels in the liver of HFD-induced obese mice.[64-66]

***Urtica dioica* L.:** There are studies that reveal the effects of nettle against fatty liver both ethnobotanical and animal experiments. The lipid profile was investigated in hypercholesterolemic rats. *Urtica dioica* extract was given for 4 weeks and decreased blood lipid levels were observed.[8,67]

***Vaccinium vitis-idea* L.:** Its fruits are quite successful in reducing the lipid level in the blood according to the experimental results. The effect of *V. vitis-idea* supplementation on liver damage was investigated. It also reduced hepatic oxidative stress and aggregation of inflammatory. These results suggest that supplementation of *V. vitis-idea* may protect against liver injury, in part by attenuating hepatic lipid accumulation, oxidative stress, and inflammatory response.[68]

***Vernonia amygdalina* Delile:** It is used as a fat reducer against obesity traditionally.[20]

***Vitis vinifera* L.:** Grape is used as a lipid lowering agent in traditional medicine.[8] It is also used in ethnobotany against other liver diseases.[21] The study investigated the effect of grape skin extract (GSE) on adiposity and hepatic steatosis in mice fed an HFD, and its basic mechanisms based on adipose and hepatic lipid metabolism. GSE supplementation significantly reduced body weight, fat weight, plasma FFA level and hepatic lipid accumulation compared to the HFD group.[69] Resveratrol in grape seed is a secondary metabolite that was shown to have antihyperlipidemic, antiobesity, and fatty liver activities in clinical studies and animal experiments.[36]

***Zingiber officinale* L.:** It was hypothesized that ginger inhibits NAFLD, blunts its progression through several mechanisms, including activating the peroxisome proliferator-activated receptor, which induces adiponectin and down-regulates proinflammatory cytokines, altering the balance between adiponectin and tumor necrosis. The activity mechanisms are thought to have interesting potentials for ginger to serve as a natural supplement for the prevention and treatment of NAFLD.[70] Also it is used as an antiobesity agent in ethnobotanical usage.[20]

In this review study, the traditional use of medicinal plants in fatty liver disease and the results of experimental studies were prepared. Especially recently, the data obtained by scanning PubMed, Wos, ChemAbst, Scholar etc. sources were compiled.

CONCLUSION

Fatty liver is a problem associated with obesity and is a worldwide health issue. Although an effective treatment protocol against fatty liver is not declared, it is thought that lipid-lowering and fat-burning metabolites may also be effective against fatty liver. Herbal preparations were used in the treatment and prevention of many diseases since ancient times. In this context, plants are frequently used in the treatment and prevention of liver diseases. In this study, information on plant formulations used in the traditional treatment of liver diseases worldwide and information on extracts and natural compounds that are effective against fatty liver in the literature are given. As can be understood from the study, plant preparations and their derived products may have a broad preventive/therapeutic potential against fatty liver disease. More detailed clinical data need to be reviewed with meta-analyses on the topic of interest.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise,

working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ayşe Esra Karadağ, Fatih Demirci;* ***Design:*** *Ayşe Esra Karadağ, Fatih Demirci;* ***Control/Supervision:*** *Ayşe Esra Karadağ, Fatih Demirci;* ***Data Collection and/or Processing:*** *Ayşe Esra Karadağ;* ***Analysis and/or Interpretation:*** *Ayşe Esra Karadağ, Fatih Demirci;* ***Literature Review:*** *Ayşe Esra Karadağ;* ***Writing the Article:*** *Ayşe Esra Karadağ, Fatih Demirci;* ***Critical Review:*** *Fatih Demirci;* ***References and Fundings:*** *Fatih Demirci;* ***Materials:*** *Ayşe Esra Karadağ, Fatih Demirci.*

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