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REVIEW

Persian Medicine

Effects of chicory (*Cichorium intybus* L.) on nonalcoholic fatty liver disease

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Highlights

The purpose of this study is to investigate the recent studies and findings on the effects of chicory (*Cichorium intybus* L.) on nonalcoholic fatty liver disease-related factors, such as dyslipidemia, oxidative stress, insulin resistance, obesity, and chronic inflammation, and disclose their underlying mechanisms.

Traditionality

Chicory (*Cichorium intybus* L.) is a part of the Asteraceae family (tribe of Lactuceae) and a medicinal food known as chicory now. The use of chicory dates to ancient Egypt, but the plant was used even before it was identified. The Egyptians cultivated chicory as a medicinal plant 4,000 years ago. They believed that the plant could help in purifying the blood and liver and treat heart disease. Horace's Roman poem is one of the first references that recommended chicory consumption (65−8 B.C.E.). Its great importance can attribute to the fact that Avicenna had written a treatise on chicory and its properties. Chicory was transported from Europe to North America in the 1700s. In the early 17th century, chicory was started as an animal feed in Northern Europe. In 2000, the French Food Safety Agency confirmed that inulin is an ingredient of chicory, and it increases the proliferation of intestinal flora. Chicory was used as a coffee substitute during the Napoleonic Era. Evidence suggests that the soldiers used it in the American Civil War. This plant has been introduced as a native plant to the regions of Western Asia, Europe, and North Africa by the Food and Agriculture Organization.

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Abstract

There is a dramatic increase in the prevalence of nonalcoholic fatty liver disease, which is slowly turning into a pandemic as well as a major challenge across the world. Nonalcoholic fatty liver disease is described as a range of liver conditions such as fat accumulation, hepatic steatosis, or end-stage liver disease. Patients with nonalcoholic fatty liver disease are asymptomatic and their mortality is higher than people without nonalcoholic fatty liver disease. The pathogenesis of nonalcoholic fatty liver disease has not been clearly determined yet. The "two hits" hypothesis is designed to explain the pathogenesis of nonalcoholic fatty liver disease. Dyslipidemia, oxidative stress, insulin resistance, obesity, and chronic inflammation are some of the morbidities involved in the progression of nonalcoholic fatty liver disease. Chicory (*Cichorium intybus* L.) is an herbaceous perennial, known as chicory. Chicory contains various compounds, such as vitamins, sonchuside A, caffeic acid derivatives, fructo-oligosaccharides, chlorogenic acid, magnolialide, polysaccharides, coumarins, phenolic acids, terpenoids, flavonoids, polyphenol, cichoriosides, ixerisosides, eudesmanolides, inulin, bitter sesquiterpene lactones, and alkaloids. Current research has revealed that chicory supplementation might be effective in the treatment of nonalcoholic fatty liver disease. The anti-inflammatory, antihepatotoxic, antihyperlipidemic, antidiabetic, antihyperglycemic, and antioxidant properties of chicory provide plausible mechanisms by which chicory may affect the various steps of disease progression and severity. Existing studies have shown that chicory supplementation has beneficial effects on nonalcoholic fatty liver disease, but the existence of only one human study and possible side effects of chicory necessitate further studies.

Keywords: Nonalcoholic fatty liver disease, Two hits, Chicory (*Cichorium intybus* L.), Inflammation, Oxidative stress

***Author contributions*:**

Samira Faraji and Mohammad Alizadeh conceived the study, Samira Faraji conducted literature review and wrote the manuscript, Mohammad Alizadeh and Sevana Daneghian critically revised the manuscript; and all authors read and approved the final manuscript.

***Abbreviations*:**

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis, T2DM, type 2 diabetes mellitus; TG, triglycerides; TNF-α, tumor necrosis factor alpha; RCT, randomized control trial; FFAs, free fatty acids; IL-6, interleukin 6; LDL, low-density lipoprotein.

***Competing interests*:**

The authors declare that there is no conflict of interest.

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Background

Nonalcoholic fatty liver disease (NAFLD) is gradually turning into a pandemic as well as a major challenge across the world, because of its high prevalence, difficult diagnosis, multifactor pathogenesis, and lack of suitable therapies [1]. The prevalence of this disease is 25% around the world, and its highest prevalence (31.8%) is reported in the Middle East [2]. The National Health and Nutrition Examination Survey, an eight-year study, revealed that the overall mortality in patients with NAFLD (35%) was about sevenfold as compared with the patients without NAFLD (5%) [3]. NAFLD has two different types: the first one is nonalcoholic fatty liver that is known as the accumulation of fat without hepatocellular injury; whereas the second one is the nonalcoholic steatohepatitis (NASH), which is worse than nonalcoholic fatty liver and is characterized by the accumulation of fat, as well as inflammation and injury of hepatocytes, with or without any fibrosis. NASH can progress into cirrhosis or may lead to hepatocellular carcinoma [4].

NAFLD is associated with chronic diseases such as type 2 diabetes mellitus (T2DM), metabolic syndrome, and cardiovascular diseases [5, 6]. Also, this chronic disease has a relationship with other metabolic disorders such as obesity, oxidative stress, inflammation, dysglycemia, and dyslipidemia [7, 8]. One of the most crucial hypotheses in the pathogenesis of NAFLD is the "two hits" hypothesis [9]. The "first hit" is the accumulation of lipids in the liver cells. Insulin resistance plays a role in the development of fat accumulation. Steatosis increases the uptake of fatty acids and consequently increases the production of triglycerides (TG) [10]. The "first hit" causes the disease to progress to the "second hit". Lipid peroxidation, oxidative stress, dysfunction of mitochondria, adipokines, and cytokines manifest in the second hit (Figure 1) [11].

The most commonly used medications for the treatment of NAFLD are liraglutide, dipeptidyl peptidase-4 inhibitors, metformin, thiazolidinediones, sodium-glucose transport protein 2 inhibitor, vitamin E, and sulfonylurea [12, 13]. Despite the positive therapeutic effects of abovementioned treatments, various side effects have also been reported. A study has reported gastrointestinal side effects of using liraglutide [14]. Weight gain, cardiovascular side effects, bone fractures, and peripheral edema are some of the side effects that have been demonstrated in the use of thiazolidinediones [12]. Sodium-glucose transport protein-2 inhibitors can increase the infection of urinary and genital tract [15]. Headache, hypoglycemia, infection of respiratory and urinary tracts, and nasopharyngitis have been reported after using dipeptidyl peptidase-4 inhibitors [16, 17]. Nausea, diarrhea, renal problems, and lactic acidosis are the adverse reactions of metformin [12]. Finally, sulfonylurea has a direct relationship with the risk of hepatocellular carcinoma [17].

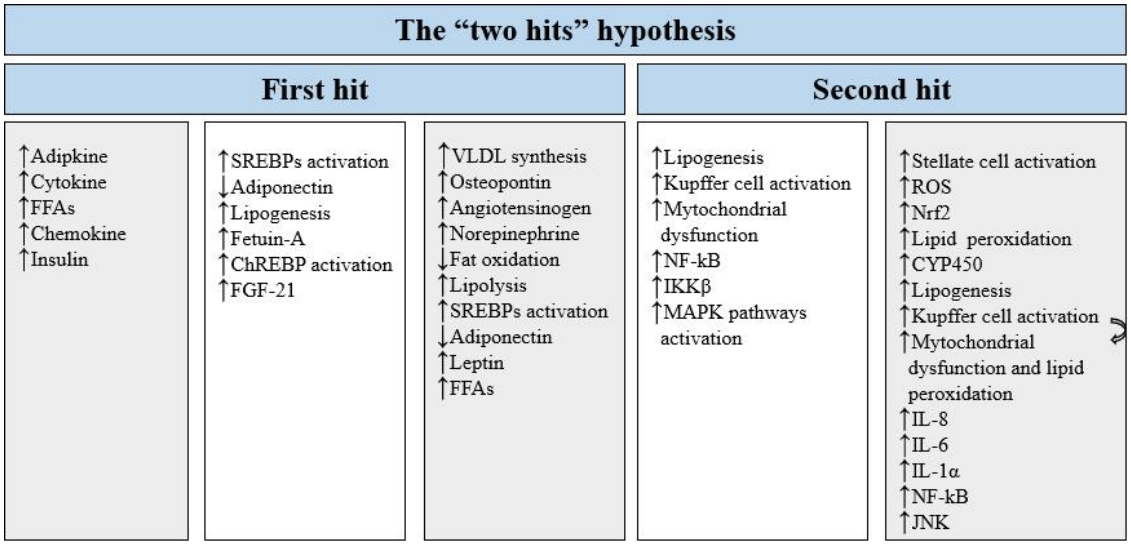

Figure 1 Two hits hypothesis. The "two hits" hypothesis is designed to explain the pathogenesis of NAFLD, with the "first hit" including fat accumulation in the liver, elevated liver enzymes, abdominal obesity, and insulin resistance; and the "second hit" including cellular stresses such as oxidative stress, fibrogenesis, and apoptosis. FFAs, free fatty acids; ChREBP, carbohydrate-responsive element-binding protein; FGF-21, fibroblast growth factor 21; SREBPs, sterol regulatory element-bindings; VLDL, very low-density lipoprotein; NF-κB, nuclear factor-κb; IKKβ, IKβ kinase β; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species; CYP450, cytochrome P450; Nrf2, nuclear factor erythroid 2-related factor 2; IL-8, interleukin 8; IL-6, interleukin 6; IL-1α, interleukin-1 alpha; JNK, c-Jun N-terminal kinase. ↑shows increase, and ↓ shows decrease.

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Therapeutic options for NAFLD are limited and herbal medicine may offer an alternative treatment for NAFLD because of the cultural, economic, and practical reasons as well as low side effects and benefits [18, 19]. The most commonly used herbal medicine for patients with NAFLD are resveratrol, Qianggan and Yiqi Sanju formulas of traditional Chinese medicine, berberine, *Phyllanthus*, soluble fibers, and silymarin/silybin [18, 20−24]. Herbal medications may have some side effects too. Moreover, the consumption of silybin can cause dysgeusia and pruritus [25]. Qianggan formula in capsule form consists of 16 herbs such as *Isatis tinctoria* L., *Paeonia lactiflora* Pall., *Radix Angelica Sinensis*, *Radix Astragalus Membranaceus*, *Radix Salviae Miltiorrhiza*, and some other components can cause nausea, burning sensation, and diarrhea [24, 26]. The consumption of berberine led to anorexia, stomach problems, diarrhea, and constipation [27]. Yiqi Sanju formula consists of *Pollen Typhae* and other herbs can cause diarrhea, as well as gastrointestinal and appetite problems [24]. *Phyllanthus* can cause dyspepsia, diarrhea, headache, bleeding of per-rectal and gums, chest pain, cough, decreased vision [28]; and, leucopoenia, and thrombocytopenia are some of the adverse effects of using resveratrol [24].

Chicory (*Cichorium intybus* L.) is a part of the Asteraceae family (tribe of Lactuceae) and a medicinal food known as chicory now [29]. The Egyptians cultivated chicory as a medicinal plant 4,000 years ago [30]. They believed that the plant could help in purifying the blood and liver and treat heart disease. Horace's Roman poem is one of the first references that recommended the consumption of chicory (65−8 B.C.E.). Its great importance can attribute to the fact that Avicenna has written a treatise on chicory and its properties (691 C.E.). Chicory was transported from Europe to North America in the 1700s. In the early 17th century, chicory was started as an animal feed in Northern Europe. In 2000, the French Food Safety Agency confirmed that inulin is an ingredient of chicory, and it increases the proliferation of intestinal flora. Chicory was used as a substitute of coffee during the Napoleonic Era. Evidence suggests that the soldiers used it in the American Civil War. Also, the chicory root was used in the United States instead of bean drinks. This plant has been introduced as a native plant to the regions of Western Asia, Europe, and North Africa by the Food and Agriculture Organization [31]. Literature has shown that the important constituents of chicory are vitamins, sonchuside A, caffeic acid derivatives, fructo-oligosaccharides, chlorogenic acid, magnolialide, polysaccharides, coumarins, phenolic acids, terpenoids, flavonoids, polyphenol, cichoriosides, ixerisosides, eudesmanolides, inulin, bitter sesquiterpene lactones, and alkaloids [22, 23, 29]. Chicory has antioxidant, antibacterial, antipyretic, antidiabetic, antihepatotoxic, anti-inflammatory, antiulcerogenic (root), antihyperglycemic, and antihyperlipidemic, anticancer and antimalarial activities, which have been successfully demonstrated in several studies [29, 32−37]. The purpose of this study is to investigate the recent studies and findings on the effects of chicory on the NAFLD-related factors.

The effect of chicory on obesity and NAFLD

Obesity is an increasingly significant public health issue in the world [38, 39]. The degree of obesity (excess weight, obese, and severely obese) is closely associated with NAFLD, and it is a strong risk factor for a lot of entities, including NAFLD [8, 40]. The prevalence of NAFLD in people with obesity is reported to be about 80% [41, 42]. Weight loss and exercise are the most essential lifestyle changes for the management and treatment of patients with NAFLD [43, 44]. The effect of body weight loss on the treatment of NAFLD is related to the amount of weight loss. Up to 7−10% of weight loss should be the primary aim of patients but even 3−5% of weight loss can improve steatosis, more than 5% can decrease inflammation, more than 7% can cause a notable decrease in steatohepatitis, and 10% or more weight reduction is suitable for the treatment of fibrosis [45].

In addition, obesity is strongly linked to insulin resistance and high inflammatory markers such as interleukin-1 and tumor necrosis factor alpha (TNF-α); therefore, weight loss may decrease these factors and can improve NAFLD in this way [5]. Also, Sookoian et al. discovered that fibrosis score and NAFLD activity score were higher in patients with both obesity and NAFLD [46].

Many researchers have studied the effects of consumption of chicory in patients with NAFLD on body composition [33, 47−50]. In some human and animal studies, the authors have shown that chicory can lead to weight loss [47, 48]. Presumably, there is no human randomized control trial (RCT) study, except the study of Ghaffari et al. that examined the effects of chicory seed and turmeric supplementation on patients with NAFLD [21]. In the abovementioned study of 2019, there was a decrease in waist circumference, weight, and body mass index in patients who used chicory and turmeric plus chicory as compared to placebo ($P < 0.05$) [21]. In only two animal studies, chicory supplementation in rats significantly reduced the weight. A study conducted by Cho et al. in 2010, showed that after an intervention of 14 days, the supplementation of chlorogenic acid and caffeic acid, the two important constituents of chicory, decreased weight and visceral fat mass in eight male mice [47]. In addition, weight had a correlation with insulin ($P < 0.01$) and leptin ($P < 0.01$). Even in this study, the effect of chlorogenic acid was more effective than caffeic acid in reducing the body weight

and regulating the lipid metabolism. In the study of Wu et al., 48 male Sprague Dawley rats received chicory supplementation and a high fat diet (fat = 45%) for four days [33]. After the intervention, their body weights changed significantly. However, a study of 46 patients with diabetes showed that there was not any difference in the body weight between two groups after supplementing a daily dose of 10 g of chicory for 2 months [48]. According to the inconsistent results of the abovementioned and some other studies, chicory supplementation is likely to have a positive effect on weight [49, 50].

The effect of chicory on insulin resistance and NAFLD

The development of NASH conforms to the "two hits" hypothesis. The "first hit" involves the accumulation of fat in the liver and dysglycemia, whereas the "second hit" includes cellular stresses such as oxidative stress-mediated inflammation, fibrogenesis, and apoptosis [9, 10]. The prevalence of NAFLD in patients with diabetes has not exactly been known. Recent studies have shown that the prevalence of NAFLD in patients with diabetes has been increased rapidly over the past two decades worldwide as compared with the individuals without diabetes [51, 52]. The several lines of evidence have estimated that the prevalence rates of NASH and fibrosis in patients with diabetes and NAFLD are approximately 69.2% and 41.0%, respectively [53]. There is a bidirectional association between NAFLD and T2DM, in which NAFLD appears to enhance the risk for T2DM, and T2DM may promote NAFLD progression; however, additional investigation is needed to determine accurate results [8]. Putting together, it can be stated that there is a relationship between NAFLD and insulin resistance [54].

There is no human RCT study, except the study by Ghaffari et al. that examined the effects of consumption of chicory seed and turmeric on insulin resistance in patients with NAFLD [21]. After 12 weeks of intervention, homeostatic model assessment for insulin resistance decreased in both groups that received chicory seed only (9 g/d (4.5 g/100 mL)) and that received turmeric with chicory seed (3 g/d turmeric plus infused 9 g/d chicory seed). It should be noted that in one animal study by Ghamarian et al., the level of glycated hemoglobin A1c and fasting blood sugar decreased significantly after 28 days of chicory extract injections (125 mg/kg body weight), but in the group of rats with early-stage diabetes, unlike late-stage diabetes, fasting serum insulin concentration were higher at the end of the study [55]. Apart from that, in another animal study that was conducted on 32 high-fat-diet-induced obese mice, the insulin levels decreased after 14 days supplementation of caffeic acid and chlorogenic acid [47]. In another study, 46 female patients with diabetes were divided into two groups: the first was placebo (n = 22) and the second was intervention group that received enriched treatment of chicory (n = 27) in form of a daily dose of 10 g of chicory. In this study after two months, the fasting serum glucose levels decreased in the intervention group [48]. As previously suggested by others, the antihyperglycemic effect of chicory has been reported in other experiments about ferulic, caffeic, and chicoric acids in roots of chicory [56, 57]. Because of the lack of human studies to investigate the effect of this traditional medicine plant on fatty liver, there is an urgent need of more human studies. However, it should be noted that the studies should consider all the possible side effects of chicory.

The effect of chicory on dyslipidemia and NAFLD

According to the "two hits" hypothesis, NAFLD is related to the excess levels of triacylglycerol in liver, which is known as steatosis [58]. This condition may occur because of a problem in any of the pathways that are related to the delivery, synthesis, export, or oxidation of triacylglycerol, synthesis of very low-density lipoprotein, increased lipolysis, and liver free fatty acids (FFAs) uptake, which had mentioned in the "first hit" [54, 59]. Circulating FFAs, which represent the main source of hepatic fat accumulation, are originated from lipolysis [60].

As a consequence, patients with NAFLD usually have high TG, increased very low-density lipoprotein, and high apolipoprotein B-to-apolipoprotein A‐1 ratio, as well as a higher concentration of small dense LDL coupled with low high‐density lipoprotein concentration [7, 61]. On the contrary, saturated fatty acids activate the path of the c-Jun terminal kinase and contribute to the development of hepatic steatosis and insulin resistance [62].

The prevalence of dyslipidemia (hypercholesterolemia, hypertriglyceridemia, or both) in individuals with NAFLD has been estimated to be between 20% and 80% [63]. Other studies on prevalence of NAFLD in individuals with dyslipidemia had demonstrated, more than 50% of individuals with abnormality in amount of lipids have NAFLD [8, 33]. Recently, it is presented that the "two hits" hypothesis is outdated, but still it can explain the mechanism of lipotoxicity in NAFLD, in the best way.

Notably, sterol regulatory element-binding proteins can regulate the lipid metabolism [64]. Previous studies have shown that 28 days of chicory seed extract supplementation in male Wistar rats significantly decreased sterol regulatory element-binding proteins-1c and peroxisome proliferator-activated receptor alpha levels [65].

Based on the evidence, several studies have shown that chicory can affect lipid profiles [21, 33, 47, 50].

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But, in the study conducted by Ghaffari et al., chicory seed supplementation as long as 12 weeks had no effect on the lipid profile in the chicory seed group [21]. In this study, subjects were divided into four groups: the first group received (3 g/d) turmeric, the second group received (9 g/d) chicory seed, the third group received turmeric (3 g/d) plus chicory seed supplementation (9 g/d), and the fourth group received placebo. In the turmeric group and turmeric plus chicory seed group, total cholesterol, LDL-cholesterol, and TG levels decreased significantly after the end of the treatment. The significance of lipid profile changes in turmeric group and turmeric plus chicory group as compared to chicory group can be attributed to the turmeric effect in both groups.

In another study, after supplementation with caffeoylquinic acid as a chicory extracted ingredient, no effect was observed on the lipid profile [66]. The method of investigation that lasted for 28 days was as follows: (1) during the first two weeks of feeding, rats were on a high cholesterol and fructose diet; (2) in the second two weeks, the diet of rats was high on caffeoylquinic acid. Probably other components of chicory have the ability to change lipid profile. In two studies related to this issue, Zhu et al. in 2019 and Wu et al. in 2018 found that chicory supplementation in rats decreased the total cholesterol, TG, and LDL and increased high - density lipoprotein levels [33, 50]. In another study by Cho et al., caffeic acid and chlorogenic acid caused a positive effect on TG and cholesterol levels after 14 days [47]. According to the results reported above and other available studies, the positive effects of chicory have been observed on lipid metabolism [55, 67]. In summary, there is considerable evidence that links chicory supplementation with lipid homeostasis and NAFLD.

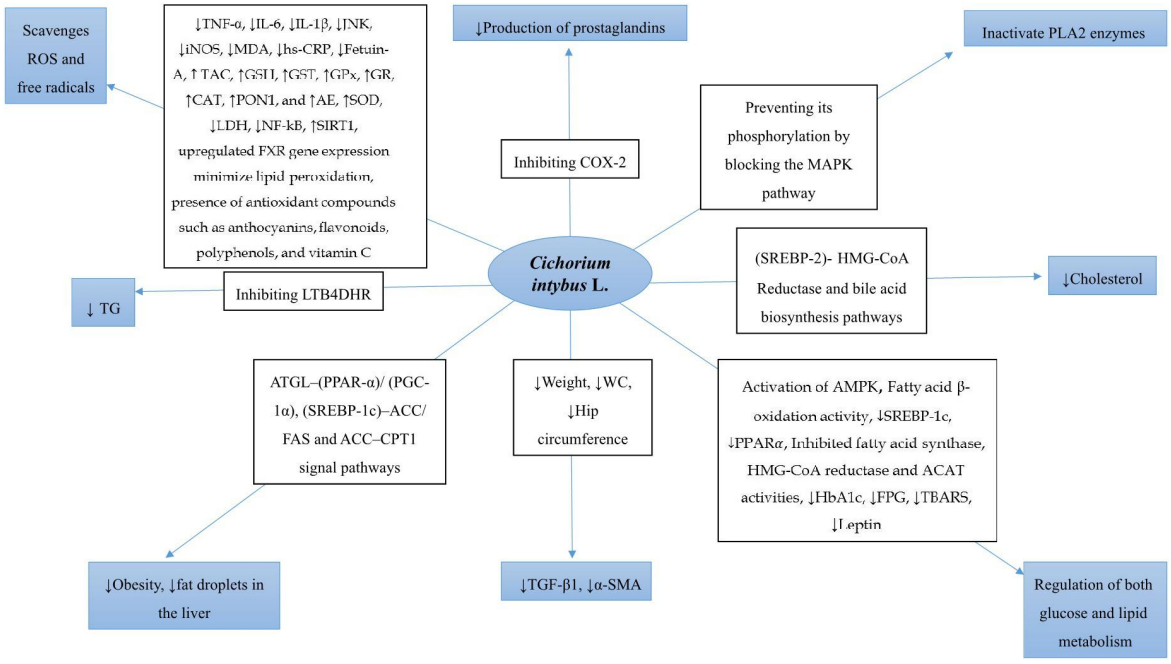

Figure 2 Relationship between *Cichorium intybus* L. and the NAFLD-related factors. ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; IL-1β, interleukin 1 beta; JNK, c-Jun N-terminal kinase; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; hs-CRP, high-sensitivity C-reactive protein; TAC, total antioxidant capacity; GSH, glutathione; GST, glutathione S-transferase; GPx, glutathione peroxidase; GR, glutathione reductase; CAT, catalase; PON1, paraoxonase 1; AE, arylesterase; SOD, superoxide dismutase; LDH, lactate dehydrogenase; NF-κB, nuclear factor-κb; SIRT1, sirtuin 1; FXR, farnesoid - X - receptor; Cox-2, cyclooxygenase-2; PLA2, phospholipase A2; MAPK, mitogen-activated protein kinase; SREBP-2, sterol regulatory element-binding protein 2; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; AMPK, adenosine 5'-monophosphate-activated protein kinase; SREBP-1c, sterol regulatory element-binding protein-1c; PPAR-α, peroxisome proliferator-activated receptor alpha; ACAT, acyl-coenzyme A cholesterol acyltransferase; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; TBARS, thiobarbituric acid-reactive substances; TGF-β1, transforming growth factor-β1; α-SMA, alpha-smooth muscle actin; WC, waist circumference; ATGL, adipose triglyceride lipase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; CPT1, carnitine palmitoyl transferase I; TG, triacylglycerol; LTB4DHR, leukotriene B4 dehydrogenase. ↑shows increase, and ↓ shows decrease.

The effect of chicory on inflammation and NAFLD

According to the second hit in the "two hits" model, systemic chronic inflammation plays a basic role in the pathogenesis of NAFLD, because the increasing levels of proinflammatory cytokines can increase the risk of NAFLD [68]. The accumulation of lipids in the hepatocytes leads to redox imbalance and fat oxidation, thereby causing the inflammatory response of proinflammatory cytokines such as high-sensitivity C-reactive protein and TNF-α [69]. Among the inflammatory markers, TNF-α and interleukin 6 (IL-6) play a basic role in causing the inflammation [70−73]. TNF-α plays a role in both the early and later stages of NAFLD [73−76]. Different studies have shown a direct association of TNF-α expression with the severity of NAFLD and degree of fibrosis in patients with NASH [21, 69, 70]. Studies conducted on humans have showed that the expression of IL-6 is related to the degree of inflammation and fibrosis [21, 77]. It should be noted that the contribution of liver in the construction of the IL-6 is presently unclear. Moreover, the adipose tissue is currently one of the main production sites for IL-6 [78].

Different animal studies have shown the role of IKβ Kinase β and NF-κB signaling in NAFLD, but these studies do not have strong findings for humans [79]. One clinical study found that the expression of nuclear factor-Kb p65 was increased in the patients with NAFLD (20 patients with NASH, 40 patients with alcoholic steatohepatitis); however, further research is needed to determine the role of this pathway in the patients with NAFLD [80].

In searching for the anti-inflammatory activity of chicory, Cavin et al. found that the extract of chicory and ethyl acetate can suppress TNF-α and prostaglandin E2 in the human colon HT29 cells, respectively [81]. The study of Ghaffari et al. demonstrated that the supplementation of chicory seeds (infused 9 g/d (4.5 g/100 mL)) for 12 weeks significantly decreased the level of TNF-α [21]. The levels of high-sensitivity C-reactive protein and IL-6 decreased significantly in the participants that received turmeric and chicory seed supplements as well. The individuals were 92 patients with NAFLD aged 20−60 years old (body mass index = 24.9−40 kg/m^2). Various mechanisms suggest that chicory appears to have an anti-inflammatory activity, but there is no study on the effects of different parts of chicory on the inflammation; therefore, further human and animal studies are needed.

The effect of chicory on oxidative stress and NAFLD

The role of oxidative stress in NASH and NAFLD is described in the "two hits" hypothesis [68]. Oxidative stress is caused by a cellular imbalance and production of reactive oxygen species [82, 83]. In these conditions, the increased lipid peroxidation leads to the activation of liver stellate cells and, thus, to fibrogenesis [82, 83]. Reactive oxygen species are main intermediates of inflammation [82]. As a consequence, FFAs, inflammatory factors, and TNF-α lead to oxidative stress [53, 84]. Indeed, several studies have a strong relation between the severity of NASH and the degree of oxidative stress [85].

Ghaffari et al.'s study is the only study that found the relationship between chicory supplementation and oxidative stress indicators [21]. Their mentioned study found that malondialdehyde were decreased and the total antioxidant capacity levels were increased significantly after chicory intake. The relationship between chicory and improvement in the blood antioxidant status are noted in a majority of animal studies [33, 34, 50, 66, 86, 87]. Only in one study conducted by Saggu et al., rats that used 4-tert-octylphenol for 8 weeks had decreased glutathione, superoxide dismutase, and catalase levels, whereas a reduction in thiobarbituric acid-reactive substances recorded in the rats that received chicory fruit extract with 4-tert-octylphenol [49]. The observed results mean that the chicory fruit extract could improve the abnormalities resulting from 4-tert-octylphenol by decreasing thiobarbituric acid-reactive substances and the pronounced improvement of the investigated biochemical and antioxidant parameters. These mentioned studies justify and validate the antilipid peroxidation and antioxidant effects of chicory.

Possible side effects of chicory

Despite the positive effects of chicory on NAFLD, like other treatments for NAFLD, the possibility of adverse effects for this herbal treatment is not unthinkable, but only one study by Farhangi et al. has shown some side effects of using this plant after two months [48]. They evaluated the effects of chicory inulin on the enzymes of liver, metabolism of calcium, and blood factors in women with T2DM. In this study, chicory significantly decreased hematocrit and mean corpuscular volume ($P < 0.05$).

Conclusion

Due to the "two hits" hypothesis of NAFLD pathogenesis, NAFLD is related to dysglycemia, dyslipidemia, oxidative stress, inflammation, and obesity [88]. The anti-inflammatory, antihepatotoxic, antihyperlipidemic, antidiabetic, antihyperglycemic, and antioxidant properties of chicory provide plausible mechanisms by which chicory may affect the various steps of disease progression and severity (Figure 2).

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The current research has suggested that chicory supplementation might be effective in the treatment of NAFLD. However, there are two reasons that justify the need for a more well-designed research in humans. First, RCTs investigating the effects of chicory on NAFLD are limited and there is only one study that had been conducted on patients with NAFLD [21]. Second, despite the positive effects of chicory, the evaluation of possible side effects by RCTs is necessary.

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