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Review article

The impact of Chicory (*Cichorium intybus*) on metabolic syndrome: a narrative review

Amir Behrouzian[1], Mohsen Imenshahidi[2,3], Maryam Rameshrad[2,3], Hossein Hosseinzadeh[2,3,*]

[1]*Student research Committee, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

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**** Corresponding Author:***
Tel: +98 51 31801193
Fax: +98 51 38823251
hosseinzadehh@mums.ac.ir

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Abstract

Objective: Metabolic syndrome is a medical condition identified by the presence of a cluster of factors including hyperglycemia, inflammation, hypertriglyceridemia, dyslipidemia, coagulopathies, abdominal obesity, and hypertension. Chicory (*Cichorium intybus* L.) is a promising candidate for managing metabolic syndrome due to its rich content of bioactive compounds such as inulin, sesquiterpene lactones, and polyphenols which exhibit anti-inflammatory, antioxidant, and insulin-sensitizing properties. This review aims to provide a comprehensive literature review regarding its mechanistic pathways and efficacy in the management of metabolic syndrome.

Materials and Methods: This narrative review examined studies published in Scopus, PubMed, Web of Science, and Google Scholar up to August 2024.

Results: Chicory exhibits anti-inflammatory, hypolipidemic, and hypotensive properties. The hypotensive property of chicory is associated with inhibiting oxidative stress, mediating vascular smooth muscle response, and regulating superoxide anion production. In addition, chicory's hypolipidemic capacity is linked to reduced acetyl-CoA carboxylase enzyme activity, as well as inhibitory effects on hydroxymethylglutaryl-CoA reductase and visfatin. Furthermore, it mitigates diabetes and obesity by enhancing glucose metabolism and inhibiting "Nucleotide-Binding Domain, Leucine-Rich–Containing Family, Pyrin Domain–Containing-3" (NLRP3) inflammasome activation, which in turn decreases Interleukin (IL)-1β release. Additionally, pro-inflammatory cytokines and oxidative stress which are involved in fat storage and hepatic triglyceride accumulation, are inhibited.

Conclusion: Numerous studies suggest chicory's potential benefits for individuals with metabolic syndrome. To fully understand its potential, we need clinical trials to confirm its efficacy, safety, and optimal dosage, thereby bridging the gap between research and practical healthcare solutions.

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Introduction

Metabolic syndrome is characterized by a complex combination of coexisting cardiac risk factors including high levels of triglycerides and cholesterol, elevated blood sugar levels (hyperglycemia), reduced levels of high-density lipoprotein cholesterol (HDL-C), abdominal obesity, and hypertension (Alberti et al. 2006). This syndrome is commonly identified through the presence of at least three of the specified risk factors (Alberti et al. 2009). There has been a rise in the consumption of high-calorie and low-fiber fast foods, coupled with a decrease in physical activity levels brought on by mechanized transportation and sedentary leisure activities, which have made metabolic syndrome a severe health risk and a global issue (Saklayen 2018). The prevalence of metabolic syndrome is approximately 20-30% of the adult population worldwide (Li et al. 2022b). Elevated chances of developing cardiovascular complications, diabetes mellitus, and other health issues are associated with metabolic syndrome, which places this disorder among the top leading contributors to global mortality rates (Saklayen 2018).

Besides drug repositioning (Maiorana et al. 2023; Radosavljevic et al. 2024; Rameshrad et al. 2019; Rameshrad et al. 2020; Wong 2021), herbal medicine has gained focus for treating metabolic syndrome components. Garlic (*Allium sativum*) (Hosseini and Hosseinzadeh 2015), rosemary *(Rosmarinus officinalis*) (Hassani et al. 2016), *Aloe vera* (Shakib et al. 2019), Chinese hawthorn (*Crataegus pinnatifida)* (Dehghani et al. 2019), *Nigella sativa* (Razavi and Hosseinzadeh 2014), *Capsicum annuum* (Sanati et al. 2018), Grapes (*Vitis vinifera*) (Akaberi and Hosseinzadeh 2016), Avocado (*Persea americana*) (Tabeshpour et al. 2017b), *Boswellia* species (Mahdian et al. 2020), okra (*Abelmoschus esculentus*) (Esmaeilzadeh et al. 2020), *Ginkgo biloba* (Eisvand et al. 2020), milk thistle (*Silybum marianum*) (Tajmohammadi et al. 2018), *Garcinia mangostana* (Tousian Shandiz et al. 2017), and *Berberis vulgaris* (Tabeshpour et al. 2017a) are some medicinal herbs proposed to have efficacy in reliving metabolic syndrome deteriorative effects by mitigating oxidative stress, increasing glucose and lipid metabolism, and decreasing insulin resistance.

Cichorium intybus (chicory) is one of the herbal species recognized for its therapeutic properties, having been used for a long time and attracting considerable attention. Chicory is classified within the Asteraceae botanical family. It typically grows between 30 and 100 cm and features a tough, hollow stem. It has lanceolate leaves without any lobes. Furthermore, chicory exhibits a variety of flower colors, including white or pink tones, as well as light blue (more common). Additionally, the flower heads of chicory generally range in width from 2 to 4 cm (Aisa et al. 2020).

Chicory contains many components, including aliphatic compounds, terpenoids, saccharides, methoxy-coumarine cichorine, flavonoids, essential oils, anthocyanins, and volatile compounds (Street et al. 2013). The primary phenolic compounds found in chicory are hydroxycinnamic acids, specifically chlorogenic and chicoric acids (Sinkovič et al. 2015). Moreover, inulin, a soluble and fermentable polysaccharide fiber, is typically sourced from chicory roots (Chaito et al. 2016).

The chemical structures of chlorogenic and chicoric acid and inulin are presented in Figure 1.

Since ancient times, chicory has been utilized for various purposes including as a substitute for coffee and forage for animals. Furthermore, in Ayurveda, Unani, and Siddha systems, it has been utilized as a medicinal herb in the treatment of diseases affecting the hepatobiliary and renal systems (Chandra 2016).

Some of the proven pharmacological effects of chicory include antimicrobial activity, anthelmintic activity, hepatoprotective activity, antidiabetic

activity, gastroprotective activity, anti-inflammatory activity, analgesic activity, antioxidant activity, tumor-inhibitory activity, and antiallergic activity (Street et al. 2013) (Figure 2).

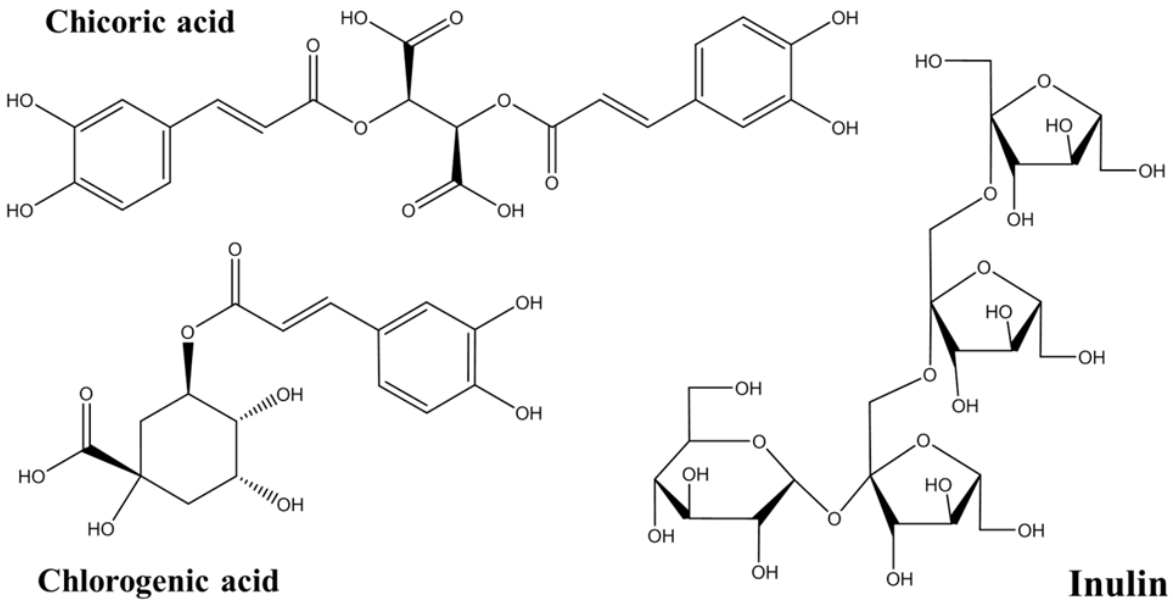

Figure 1. Chemical structures of chlorogenic acid, chicoric acid, and inulin, the main constituents of chicory.

Figure 2. Summary of therapeutic effects of *C. intybus* (chicory)

Inulin can inhibit lipid absorption, reduce the expression of sterol regulatory element binding protein (SREBP)2 and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, and regulate the metabolism of triglycerides and cholesterol. Furthermore, inulin indirectly influences lipid homeostasis by altering the composition of gut microbiota and reducing oxidative stress (Yin et al. 2024).

In this regard, chicory could be considered a promising therapeutic option for metabolic syndrome, as it contains active compounds such as inulin and phenolic compounds (with strong anti-inflammatory and antioxidant properties that play a role in reducing oxidative stress and insulin resistance) (Babaei et al. 2018; Li et al. 2022a; Neyrinck et al. 2025; Nishimura et al. 2015).

Toxicological findings in sesquiterpene lactones-enriched chicory root extract (Schmidt et al. 2007) and aqueous extract of *C. intybus* seeds (Chandra et al. 2018) demonstrated the absence of subacute or chronic toxicity at higher doses, respectively. It is important to note that Schmidt and colleagues evaluated a 28-day sub-chronic toxicity study of sesquiterpene lactones-enriched chicory root extract in both sexes of Sprague–Dawley rats. The conclusion was that oral administration of

70, 350, or 1000 mg/kg/day did not result in any treatment-related adverse effects. Furthermore, the Ames test results showed no mutagenic properties for this extract (Schmidt et al. 2007). Consistently, Chandra et al. (2018) demonstrated in both male and female Wistar rats that subacute (28-day) and chronic (90-day) oral administration of the aqueous extract of *C. intybus* seeds at doses up to 600 mg/kg/day did not cause mortality, clinical signs of toxicity, or adverse clinical effects. Body weight, food and water intake, as well as hematological and biochemical parameters (including hemoglobin, liver enzymes, creatinine, total protein, albumin, and cholesterol) showed no significant differences compared with the control group. Histopathological examination of vital organs (liver and kidney) also revealed no abnormalities in treated animals (Chandra et al. 2018).

Chicory needs a focused review due to its unique phytochemical profile, which includes inulin, sesquiterpene lactones, and phenolic compounds, all of which demonstrated significant potential in modulating key pathways involved in metabolic syndrome, such as lipid metabolism, oxidative stress, and insulin resistance (Babaei et al. 2018; Li et al. 2022a; Neyrinck et al. 2025; Nishimura et al. 2015; Yin et al. 2024). Despite growing preclinical evidence, a systematic evaluation of its therapeutic efficacy and mechanistic insights in human studies remains limited. This review consolidates existing data, highlights clinical gaps, and underscores chicory's viability as a natural intervention for metabolic disorders. This review aims to present a comprehensive summary of a range of *in vitro* and *in vivo* research investigations conducted on both animal models and human subjects, to elucidate the potential mechanisms by which *C. intybus* could impact metabolic syndrome.

Materials and Methods

In this narrative review, an extensive investigation was conducted utilizing a variety of databases, including Scopus, PubMed, Web of Science, and Google Scholar, with no time restrictions from their inception until August 2024. Furthermore, bibliographies of eligible articles were examined for additional relevant studies. The search keywords included "*Cichorium intybus*", "chicory", "metabolic syndrome", "hyperlipidemia", "atherosclerosis", "hypertension", "hyperglycemia", "obesity", "antidiabetic", "antihyperlipidemic", and "hypoglycemic".

According to the inclusion and exclusion criteria, only research articles were included, and all non-English articles were entirely excluded. Duplicate articles were removed, and only one eligible study was ultimately included. In addition, studies involving polyherbal formulations containing chicory or its constituents, as well as those on the other species of chicory, were excluded. Review articles, conference abstracts, and dissertations were also omitted from our assessment. However, these limitations were not considered in writing the Introduction or the Discussion parts.

Articles were screened independently by two researchers. In cases where there was disagreement between the two reviewers about the suitability of an article, the Corresponding author made the final decision after careful review to ensure the consistency and quality of the study selection.

In this narrative review study, quality and risk of bias assessments were not performed. The screening process for articles was conducted by examining the title, abstract, and full text based on predetermined criteria. First, the titles, then the abstracts, and finally the full text of the articles were reviewed based on the inclusion and exclusion criteria. After extraction, key information was categorized and analyzed in a specific format.

The gathered results are categorized into four main headings, with three *in vitro*, *in vivo*, and clinical studies sub-headings. Further, studies are included based on their related mechanisms within each sub-heading. A conclusion is included at the end of each part.

Results

Dyslipidemia and atherosclerosis

In vitro studies

Chicoric acid prevents the malfunctioning of "human umbilical vein endothelial cells" (HUVECs) caused by oxidized low-density lipoprotein (ox-LDL). Chicoric acid reverses ox-LDL-inhibited endothelial nitric oxide (NO) synthase phosphorylation and activation. It has been found to reduce the apoptotic effects of ox-LDL, which include maintaining the stability of the mitochondrial membrane potential and decreasing Bax activation. Chicoric acid decreases THP-1 monocytic cell attachment and lowers adhesion molecules. It also inhibits the activation of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in human cells (Tsai et al. 2017). *C. intybus* leaves were found to contain chicoric acid (Heimler et al. 2007).

Animal studies

Decreasing acetyl-CoA carboxylase enzyme, visfatin, and HMG-CoA activity

Keshk and Noeman (2015) demonstrated that chicory has atheroprotective effects. It has been reported that incorporating chicory into the rat diet at a constant rate of 10 g per 100 g had a significant impact on the lipid profile. It reduces dyslipidemia by regulating cholesterol production, vascular inflammation, and redox status. A chicory-supplemented diet reduced visfatin levels, as well as hepatic and cardiac acetyl-CoA carboxylase (ACC) activity. It also decreased the messenger RNA (mRNA) level of HMG-CoA reductase and atherogenic indices such as total cholesterol, triacylglycerol, and LDL-C. Additionally, there was a notable increase in catalase, superoxide dismutase, and paraoxonase-1 activity (Keshk and Noeman 2015).

Based on Meng et al.'s study in 2024, chlorogenic acid showed a significant ability to reduce blood lipid levels and body weight in mice. Furthermore, it has been demonstrated that chlorogenic acid inhibits the nuclear aggregation of SREBP2 and pregnane X receptor (PXR). Further, it decreased the gene expression of Niemann-Pick C1-like 1 and HMG-CoA reductase (Meng et al. 2024a).

Cholesterol homeostasis and anti-oxidative property

It has been demonstrated that chicory reduces the content and phenotype of lesional macrophages in ApoE lipoprotein-deficient mice. Consuming chicory decreased cholesterol levels and reduced oxidative stress in peritoneal macrophages and inflammation indicators, including the suppression of nuclear factor-κB. This was accompanied by an increase in the expression of ATP-binding cassette transporters A1 and G1 (ABCA1 and ABCG1), which are widely expressed in several tissues and play a crucial role in maintaining cholesterol homeostasis (Lin et al. 2015). Consuming chicory increased the transcription of ABCA1/G1 while reducing the cholesterol content in the aorta. Chicory consumption dramatically lowered the concentrations of superoxide and reactive oxygen species (ROS) in mouse peritoneal macrophages (MPMs). Consumption of chicory resulted in the inhibition of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase activity in MPMs. When compared to the control treatment, chicory consumption increased the mRNA expression of antioxidant enzymes, including glutathione reductase, catalase, superoxide dismutase, and glutathione peroxidase, decreased the amount of oxidized glutathione (GSSG),

and increased the ratio of glutathione (GSH) to glutathione disulfide (GSSG) in MPMs. It has been proposed that consuming chicory reduces cellular oxidative stress (Lin et al. 2015).

In summary, the results highlight the beneficial effects of chicory and its components, particularly chlorogenic acid, on lipid metabolism and inflammation. Chicory inhibits NADPH oxidase activity. It reduces ACC activity probably via adenosine monophosphate-activated protein kinase (AMPK) activation. Additionally, it lowers visfatin levels, an inflammatory adipocytokine, contributing to reduced cardiovascular inflammation and atherosclerosis. Further, the inhibition of SREBP2 and PXR nuclear aggregation by chlorogenic acid demonstrates chicory's role in regulating cholesterol biosynthesis and preventing liver steatosis (Table 1). Overall, these findings suggest that chicory could be a promising therapeutic agent in managing dyslipidemia and associated cardiovascular risks.

Hypertension

Animal studies

Antioxidant property

Elgharabawy et al. conducted a study on albino rats and found that the group exposed to lead oxide nanoparticles exhibited heart damage and higher oxidative stress. However, the administration of chicory was able to reverse these effects. The study found that by scavenging free radicals, chicory could reduce the heart damage caused by lead oxide nanoparticles (Elgharabawy et al. 2021).

The administration of chicory extract at a specific dosage demonstrated significant hypotensive effects in normotensive rats, suggesting its potential therapeutic value in the management of hypertension. However, the results also acknowledge conflicting views on the effectiveness of antioxidant supplementation in treating hypertension, mainly due to the pro-oxidant properties that some antioxidants may exhibit at high concentrations (Sedighi et al. 2021).

In conclusion, chicory's rich antioxidant profile, especially its flavonoids, is crucial in neutralizing ROS and reducing oxidative stress (Table 2). These effects may be attributed to the dose-dependent agonist-antagonist properties of certain compounds in chicory. While promising, the complex interplay of these mechanisms underscores the need for further research to optimize chicory's therapeutic application in hypertension management.

Diabetes

In vitro studies

Inhibitory effects on enzymes involved in sugar decomposition

An *in vitro* study conducted in 2021 by Attaallah et al. showed that *C. intybus* roots inhibit α-amylase and α-glucosidase enzymes (Attaallah et al. 2021).

Antioxidant effects and protection for β-cells

According to the findings, *C. intybus* prevented mouse bone marrow macrophages from activating the nucleotide-binding Domain, Leucine-Rich Containing Family, Pyrin domain–containing–3 (NLRP3) inflammasome, which in turn reduced the release of IL-1β that may improve glucose metabolism. Also, *C. intybus* extract enhanced the M2 macrophage population while decreasing the infiltration of M1 macrophages in white adipose tissue (Shim et al. 2016).

Further, *C. intybus* methanolic extract (CME) and *C. intybus* detannified methanolic extract (CME/DT) increased glucose uptake in 3T3-L1 adipocytes in the presence of insulin, where Genitein, an insulin receptor tyrosine kinase blocker, and wortmannin, a phosphatidylinositol 3-kinase (PI3K) inhibitor, blocked the effect of CME but not CME/DT. Furthermore, CME, but not CME/DT, inhibited protein tyrosine phosphatase 1B activity. CME increased the protein levels of Insulin receptor β (IRβ), Insulin receptor substrate

(IRS) 1, and PI3K levels; CME/DT increased CCAAT/enhancer-binding protein α (C/EBPα), PPARγ, and SREBP1c mRNA expression; Both CME and CME-TE increased the gene expression of glucose transporter (GLUT)4 mRNA in 3T3-L1 adipocytes (Muthusamy et al. 2008).

The aqueous extract of *C. intybus* leaves guards against streptozotocin's ability to damage pancreatic β-cells. It provides defense by increasing the activity of antioxidant enzymes and reducing pro-oxidants. Aqueous extract of *C. intybus* leaves inhibits cytotoxicity, lowers ROS, preserves glucose-stimulated insulin secretion, and lowers NF-κB p65 translocation, according to *in vitro* data (Devi Kt and Sivalingam 2020).

The foliage and blossoms of chicory exhibit significant abilities in scavenging and reducing free radicals. Based on the findings of Dalar et al., the hydrophilic extract of chicory has an antioxidant capacity. This antioxidant feature is attributed to compounds such as caftaric, chlorogenic, and cichoric acid, as well as the flavonoid luteolin hexoside. The lyophilized aqueous leaf extract of chicory showed potential for use in suppressing metabolic syndrome as it demonstrated inhibitory effects on α-amylase, α-glucosidase, lipase, and "angiotensin converting enzyme" (ACE) *in vitro* (Dalar and Konczak 2014).

In a study conducted in 2023, Intybusin F, a novel compound, and cichoriolide I, a naturally occurring product, were among the three 12, 8-guaianolide sesquiterpene lactones that were isolated from *C. intybus* roots. These compounds have shown promising effects in aiding glucose uptake in HepG2 cells stimulated with high glucose and oleic acid. Spectroscopic analysis was used to identify these compounds. Furthermore, Intybusin F and cichoriolide I have also demonstrated inhibitory effects on NO production and reduced secretion of inflammatory cytokines in a hyperglycemic HepG2 cell model (Meng et al. 2024b).

Natural chicoric acid extract stimulated insulin release from INS-1 pancreatic β-cells and increased glucose uptake into L6 myocytes in the presence of insulin. It did not affect glucose-6-phosphatase activity in hepatic microsomes and did not impact glycogenolysis in rat hepatocytes (Azay-Milhau et al. 2013).

Animal studies

A dose of 250 mg/kg of *C. intybus* leaves extract in streptozotocin-induced diabetes maintains blood glucose levels and preserves the number and morphology of pancreatic islets (Devi Kt and Sivalingam 2020). In a study conducted by Pourfarjam et al., it was shown that the chicory seed extract exhibited a reduction in urinary α1-microglobulin excretion in the early stage of type 2 diabetes (ET2D) and decreased serum uric acid levels and glomerular diameter in the late stage of type 2 diabetes (LT2D). Streptozotocin and a combination of streptozotocin and niacinamide were used to induce diabetes in the rats. Administration of chicory seed extract decreased fasting blood sugar and blood urea nitrogen and showed improvements in the histology of kidney tissue. Chicory seed extract demonstrated an ability to repair kidney damage in the early and late stages of type 2 diabetes (Pourfarjam et al. 2017).

Increasing insulin sensitivity

In another study, it has been found that chicoric acid improved impaired glucose uptake and insulin signaling pathways. It also increased oxygen consumption and mitochondrial membrane potential. Treatment with chicoric acid improved insulin sensitivity and glucose tolerance in diet-induced obese mice and decreased weight gain. Chicoric acid treatment also restored the dysregulated expression of genes linked to glucose metabolism. In the liver and skeletal muscle of high-fat-fed obese mice, chicoric acid markedly increased the amounts of mitochondrial

DNA, citrate synthase, and ATP in addition to expressing genes linked to mitochondrial biogenesis and oxidative phosphorylation. These results suggested that by improving mitochondrial function, chicoric acid reduces insulin resistance and increases insulin sensitivity (Kim et al. 2018).

According to *in vivo* experiments on Wistar rats by Azay-Milhau et al, intraperitoneal (IP) administrations of chicoric acid extract improved glucose tolerance. Based on *in vitro* studies, this effect is likely mediated by an insulin-sensitizing mechanism and increased glucose uptake by muscles (Azay-Milhau et al. 2013).

In another study, chicory extract was found to delay the onset of complications and slow the disease's progression in rats with Type 2 diabetes mellitus, in both the late and early stages of diabetes induced by streptozotocin and a combination of streptozotocin and niacinamide, which demonstrated insulin resistance and insulin sensitivity conditions, respectively. For 28 days, the rats received daily injections of chicory extract, and their body weight and blood sugar levels during fasting were observed weekly. Insulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), NO, triacylglycerol, total protein, total cholesterol, and glycosylated hemoglobin (HbA1c) were also measured in the rats. After four weeks of treatment, chicory stopped the diabetic rats' weight loss and reduced their FBS. It also reduced ALT activity, cholesterol, triacylglycerol, and hemoglobin A1C levels, and increased blood NO concentration. In contrast to late-stage diabetes, the early-stage diabetic rats treated with chicory had higher fasting serum insulin concentrations and a glucose tolerance test (GTT) pattern close to normal (Ghamarian et al. 2012).

A study conducted by Saad et al. demonstrated that daily administration of chicory seed extract at a dosage of 250 mg/kg to streptozotocin-induced diabetic rats led to the normalization of fasting blood glucose levels, insulin levels, and insulin resistance. Additionally, chicory extracts were found to have a significant impact on testicular parameters such as sperm characteristics and testosterone levels, which are commonly affected in individuals with diabetes mellitus. Furthermore, chicory extracts were observed to reduce levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF-α), C-reactive protein (CRP), and Interleukin-6 (IL-6). These effects were achieved through the suppression of the DNA-fragmentation marker 8OHdG and caspase-3 protein levels, and the elevation of Bcl-2 protein levels (Saad et al. 2024).

Antioxidant and anti-inflammatory effect

"Growth differentiation factor 15" (GDF-15) peptide is released in response to stress. It inhibits appetite by binding to its particular receptor (Chang et al. 2020). In mice lacking GDF-15, metformin does not prevent weight gain, but it does in wild mice (Coll et al. 2020). Eltokhy et al. in a study on eighty albino mice found that chicory is a promising herbal supplement that affects GDF-15 signaling pathways to reduce inflammation, oxidative stress, and blood sugar level, and to aid in weight loss in diet-induced obesity and diabetes. Chicory significantly reduced leptin and inflammatory markers, including TNF-α and IL-6; additionally, it increased "total antioxidant capacity" (TAC) and GDF-15. All estimated markers indicated that there was no statistical difference between the groups that were treated with metformin and chicory (Eltokhy et al. 2021).

The protective effects of chicory against oxidative stress in the myocardium of diabetic mice are particularly noteworthy. Besides decreasing hyperglycemia by increasing antioxidant enzyme activity and reducing lipid peroxidation and pro-inflammatory cytokines, chicory seed extract may mitigate the cardiac-damaging effects of streptozotocin, a compound

known to induce diabetes through oxidative stress and inflammation (Sharma et al. 2019).

Chandra et al. induced diabetes in rats by a single intraperitoneal dose of streptozotocin after a five-week high-fat diet. They found that the oral administration of an aqueous extract of *C. intybus* significantly lowered serum glucose and triglyceride levels, demonstrating anti-hyperlipidemic and anti-diabetic effects, as well as antioxidant properties (Chandra et al. 2018).

Shim et al. demonstrated that the methanolic extract of *C. intybus* leaf has an inhibitory action on high-fat diet-induced type-2 diabetes and serum IL-1β levels by inhibiting serum NLRP3 inflammasome activation. It decreased the serum level of IL-1β and blood glucose. Furthermore, it decreased the gene expression of pro-inflammatory mediators (IL-1β, iNOS, TNF-α, and NLRP3) and increased the gene expression of anti-inflammatory genes (Arg1 and IL-10) in the white adipose tissue (Shim et al. 2016).

Clinical studies

According to the study by Farhangi et al., enriched chicory inulin can enhance metabolic health and decrease blood glucose in patients suffering diabetes type 2 diabetes. For two months, the control group was given a placebo, and the experimental group was administered a daily quantity of 10 grams of chicory inulin. The chicory inulin-treated group's fasting blood sugar, hemoglobin A1C, liver enzyme concentrations, and blood pressure were significantly lower. After supplementing with chicory inulin, serum calcium significantly increased; however, the group receiving a placebo showed no changes in serum calcium levels (Farhangi et al. 2016).

Chicory's pharmacological mechanisms in diabetes management are multifaceted and promising. Its primary actions, including the inhibition of α-amylase and α-glucosidase enzymes, are crucial for regulating postprandial glucose levels. The plant's potent antioxidant properties, driven by compounds like caftaric and chlorogenic acids, protect pancreatic β-cells from oxidative stress. Chicory enhances glucose uptake in adipocytes and muscle cells, potentially through modulation of insulin signaling pathways involving IRS1, PI3K, and GLUT4. Its anti-inflammatory effects, particularly inhibition of NLRP3 inflammasome and reducedIL-1β, contribute to improved glucose homeostasis. The involvement of GDF-15 signaling pathways further supports its role in blood sugar regulation and weight management (Table 3). While these mechanisms are promising, response variability necessitates further clinical research to establish chicory's therapeutic potential in diabetes treatment.

Obesity

***In vitro* studies**

Increase in AMPK phosphorylation

Chicoric acid has the potential to enhance the phosphorylation of AMPK. Also, it causes a decrease in oxidative stress through increased expression of antioxidant enzymes in HepG2 and AML-12 cells cultured in methionine- and choline-deficient medium (MCD). Additionally, chicoric acid promoted the activation of AMPK while reducing the expression of genes related to lipogenesis *in vitro*. The addition of chicoric acid to the media resulted in a slight rise in the degree of mRNA expression that anti-oxidant-related genes encode (Kim et al. 2017).

Antioxidant effects

Chicoric acid also proved effective in decreasing lipid buildup and oxidative stress in HepG2 cells exposed to palmitic acid, affecting the regulation of Nrf2 and NFκB (Ding et al. 2020).

Animal studies

Antioxidant and anti-inflammatory mechanism

Methionine- and choline-deficient diet induces nonalcoholic steatohepatitis in

mice. The introduction of chicoric acid resulted in a reduction of inflammation through the inhibition of pro-inflammatory cytokines; further, chicoric acid decreases oxidative stress, fibrosis, apoptosis, and lipogenic-related genes (Kim et al. 2017).

It has been shown that the high-fat diet (HFD) group's ultimate body weight, weight gain, and body mass index (BMI) were all noticeably higher than those of the typical diet groups. Two chicoric acid dosage supplementations (15 and 30 mg/kg) decreased body weight (8% and 16%, respectively) compared to the HFD group. Furthermore, compared to the HFD group, the chicoric acid-treated group experienced less weight gain and a lower BMI. Several factors may contribute in HFD presentation, including the reduction of AMPK phosphorylation that leads to increased lipogenesis. Additionally, increased AMPK activation leads to nuclear translocation of Nrf2 and increased expression of antioxidant genes like superoxide dismutase (SOD) and HO-1, and inhibition of the NF-κB inflammatory pathway, and a decrease in the production of pro-inflammatory cytokines that reduce oxidative stress and inflammation in nonalcoholic fatty liver disease (NAFLD). In this study, obese mice exhibited higher levels of triglycerides (TG), TC, and LDL-C/HDL-C compared to control mice. Chicoric acid supplementation enhanced these dyslipidemia-related circulation markers (Ding et al. 2020).

Numerous studies have demonstrated that phenolic compounds effectively reduce inflammation, oxidative stress, and hepatic steatosis associated with obesity in mice given an HFD; these antioxidants, like chlorogenic acid, which is available in chicory, exhibit strong anti-obesity in these mice (Cho et al. 2010).

Chicoric acid reduced alcohol-induced steatosis in mice, probably by suppressing “Inducible nitric oxide synthase” (iNOS) and tumor necrosis factor (Landmann et al. 2014).

In the research conducted by Vieira et al., female Wistar rats were fed a high-fat diet for nine weeks to induce obesity, and they were also supplemented with inulin. The results indicated that rats fed a high-fat diet exhibited cognitive deficits in learning and memory, likely due to obesity. Ultimately, while treatment with inulin did not consistently influence the animals' behavior, it did alleviate the increase in abdominal white adipose tissue and the hepatic redox imbalance caused by obesity resulting from a high-fat diet (Vieira et al. 2024).

In another study, using C57BL/6J mice given HFD, the anti-obesity impact of chicoric acid was examined. According to their initial research, mice receiving 60 mg/kg/day of chicoric acid for two months exhibited no side effects. These findings led to the selection of 15 mg/kg/day and 60 mg/kg/day of chicoric acid for this study. In contrast to mice given HFD, supplementation with chicoric acid effectively decreased body weight and weight gain, particularly when given a dosage of 60 mg/kg/day. The histological analysis revealed that after administering chicoric acid for 8 weeks, the adipocyte hypertrophy brought on by the HFD appeared to be reversed. Nevertheless, throughout the 8-week trial, no appreciable variations in food consumption were noted, indicating that chicoric acid's anti-obesity properties were not dependent on suppressing food intake. This study proposed that chicoric acid could play a significant role in preventing obesity. The findings revealed that chicory helped reduce body weight, improve hyperglycemia, and lower hepatic steatosis. Additionally, the administration of chicory resulted in decreased serum malondialdehyde levels, increased superoxide dismutase activity, and reduced concentrations of inflammatory cytokines, effectively reversing oxidative stress and inflammation in the liver (Xiao et al. 2013).

Change in gut microbiota and appetite regulating hormones

A 5-week dietary intervention in mice and 16S rRNA-based microbiota profiling revealed that roasted roots richer in inulin, sucrose, and fructose, as well as in 3-mono-O-caffeoylquinic acid and dihydrodeoxylactucin, decreased the Firmicutes/Bacteroidetes ratio. Moreover, *in vitro* digestion experiments demonstrated that this type of roasted roots of chicory significantly increased the secretion of the satiety hormones cholecystokinin and glucagon-like peptide-1 (GLP-1) (Fouré et al. 2018).

Clinical studies

Reduce ectopic fat

Weight loss maintenance is often challenging due to the association between energy deficit and body fat loss, which may lead to increased hunger and higher food consumption (Doucet et al. 2000; Sumithran et al. 2011). Ectopic fat has a significant relationship to insulin resistance (Snel et al. 2012). On the other hand, glucagon-like peptide-1 (GLP-1) agonists can promote long-term weight loss maintenance (De Silva and Bloom 2012). Furthermore, dietary fiber has been linked to a reduction in food intake and can reduce ectopic fat, making it a widely beneficial approach to promoting public health (Wanders et al. 2011). Inulin is classified as a type of dietary fiber, and chicory root is one of the primary sources of it (Qin et al. 2023). In a clinical study on prediabetic volunteers, Guess and her colleagues detailed the outcomes of administering 30 g of inulin daily for 18 weeks, in conjunction with a 9-week weight loss program and a 9-week maintenance period. Inulin supplementation has been shown to improve weight loss and decrease ectopic fat (Guess et al. 2015).

These findings suggest various strategies for achieving and maintaining weight loss, highlighting the complex relationship between diet, specific nutrients, and the body's physiological responses. The research projects highlight the challenges of sustaining weight loss due to the body's natural reactions to reduced energy intake, which can lead to increased hunger and food consumption. Nevertheless, treatments like GLP-1 agonists and dietary fibers, particularly inulin derived from chicory root, show potential in supporting long-term weight maintenance and mitigating issues such as ectopic fat and insulin resistance. While these results highlight the promise of dietary and pharmacological strategies for weight management, the difficulties in maintaining weight loss underscore the need for additional research and tailored treatment approaches.

So, chicoric acid's ability to enhance AMPK phosphorylation, reduce inflammation, and alleviate oxidative stress underscores its therapeutic potential for improving metabolic health. By exhibiting potent antioxidant and anti-inflammatory properties, chicoric acid not only inhibits critical factors involved in fat storage and adipocyte differentiation but also creates a favorable environment for lipid metabolism. Change in gut microbiota and effect on the appetite-regulating hormone are the other promising issues in weight loss that should be considered in chicory. The evidence from *in vitro*, animal studies, and even clinical studies underscores the significance of these pharmacological actions, suggesting that targeting these pathways may offer practical strategies for managing obesity and its related health issues (Table 4). Thus, further exploration of chicory's pharmacological benefits could contribute to the development of novel interventions for obesity and its comorbidities (Figure 3).

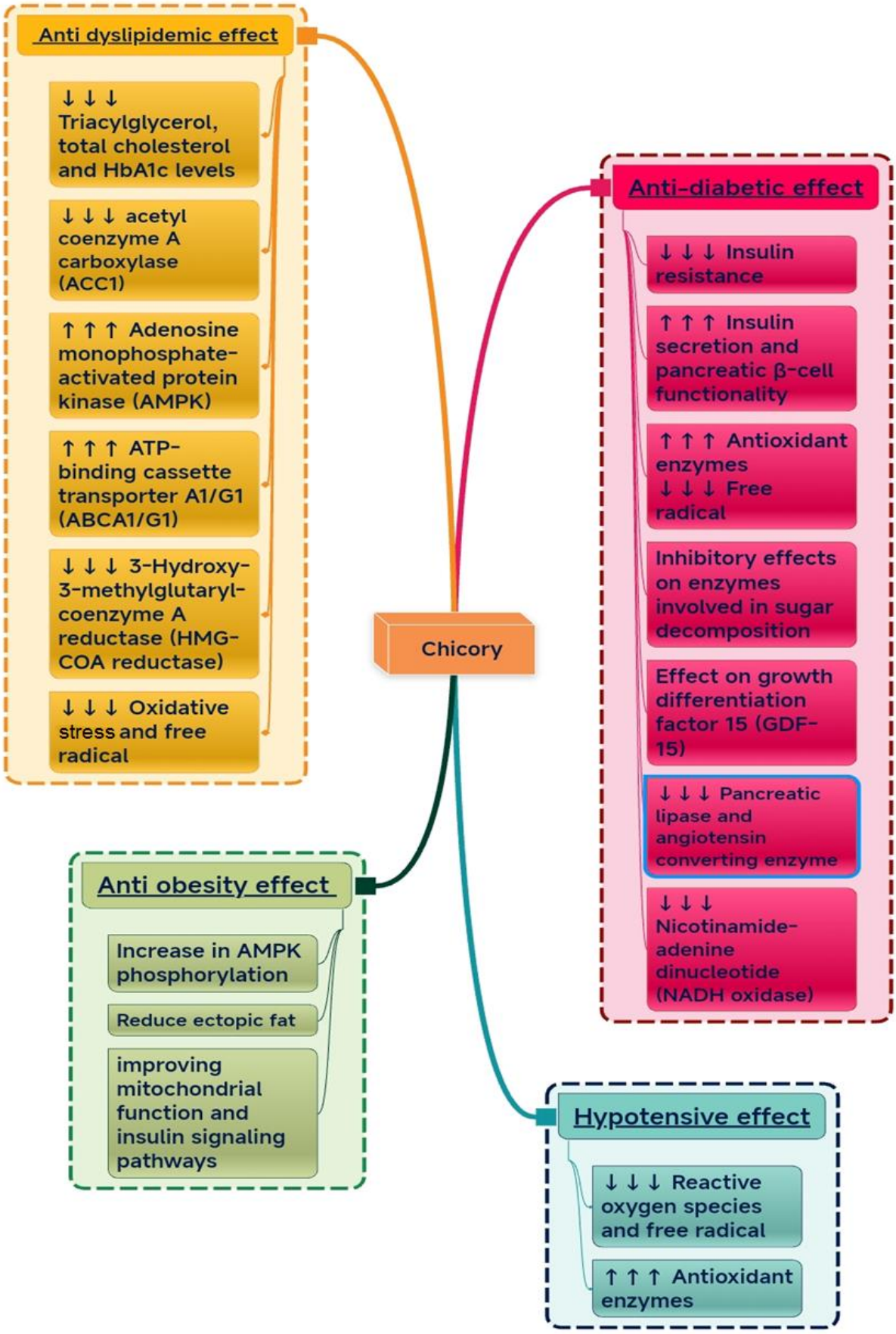

Figure 3. Schematic representation depicting the mechanisms by which *C. intybus* (chicory) contributes to the management of metabolic syndrome.

Table 1. Positive effects of chicory and its main constituents in decreasing atherosclerosis and dyslipidemia based on the type of the extract

Study type		Extract type	Plant part	Main mechanism	Ultimate effect	References
In vitro	HUVEC	chicoric acid (12.5-100 μM)	indeterminate	↑ eNOS ↓ inflammation Antioxidant effects	Anti- atherosclerosis effect	(Tsai et al. 2017)
In vivo	male albino rats (species indeterminate)	Dried powder (10% whole diet, oral, one month)	whole plant	↓ body weight ↓ dyslipidemia (↓ ACC and HMG-COA) ↓ inflammation (↓ visfatin)	↓ Dyslipidemia	(Keshk and Noeman 2015)
In vivo	male *ApoE*$^{-/-}$ mice	freeze-dried chicory (5 g/kg diet, oral, 10 weeks)	indeterminate	↑ Aortic expression of ABCA1 and ABCG1 ↓ inflammation Antioxidant effects	Anti- atherosclerosis effect	(Lin et al. 2015)

ABCA1 and ABCG1: ATP-binding cassette transporters A1 and G1; ACC: Acetyl-CoA carboxylase; eNOS: endothelial NO synthase; HMG-COA: β-Hydroxy β-methylglutaryl-CoA, NADPH: Nicotinamide adenine dinucleotide phosphate; SREBP2: sterol regulatory element-binding protein 2

Table 2. Anti-hypertensive effects of chicory and its main constituents based on the type of the extract

Study type		Extract type	Plant part	Main mechanism	Ultimate effect	References
In vivo	male Rattus norvegicus rats	hydro-alcoholic extract (100 mg/kg, gavage, four weeks)	Fruits	↓ ROS and other free radicals	Hypotensive effect	(Elgharabawy et al. 2021)
In vivo	male Sprague-Dawley rats	Ethanol extract (25, 50, or 100 mg/kg, gavage, two weeks)	leaves	↓ ROS and free radicals	anti-hypertensive effect	(Sedighi et al. 2021)

ROS: reactive oxygen species

Table 3. Anti-diabetic effects of chicory and its main constituents based on the type of the extract

Study type		Extract type	Plant part	Main mechanism	Ultimate effect	References
In vitro	biochemical tests	aqueous extracts	root	Inhibition of alpha-glucosidase and alpha-amylase	anti-diabetic effect	(Attaallah et al. 2021)
In vitro	biochemical tests	aqueous extract	leaves	Antioxidant effects α-amylase, α-glucosidase, lipase, and ACE inhibition	anti-diabetic effect	(Dalar and Konczak 2014)
In vivo	male C57BL/6 N mice	Chicoric acid (0.03%, w/w diet, oral, six weeks)	indeterminate	↑ insulin sensitivity	anti-diabetic effect	(Kim et al. 2018)
In vitro	mouse myoblast cell line C2C12	Chicoric acid (10 and 25 μM, 24 h)	indeterminate			
In vivo	male C57BL/6 mice	methanolic extract (50 mg/kg, twice a week, gavage, for six weeks)	Leaves	↓ inflammation	anti-diabetic effect	(Shim et al. 2016)
In vitro	bone marrow cell culture	methanolic extract (25, 50, and 100 μg/cc)				
In vivo	male Wistar rats	aqueous extract (125 and 250 mg/kg, oral, duration and dosage interval not mentioned exactly)	leaves	Protective effects in pancreatic islets	anti-diabetic effect	(Devi Kt and Sivalingam 2020)
in vitro	MIN6 cells (Mouse insulinoma cells)	aqueous extract (5 μg/ml and 50 μg/ml, 24 hr)				
In vivo	male Wistar rats	natural chicoric acid extract (3, 15, and 30 mg/kg/day, IP, four days)	Arial parts	insulin-sensitizing effect	anti-diabetic effect	(Azay-Milhau et al. 2013)
In vitro	rat insulinoma-derived INS-1 β-cells L6 myocyte cells isolated rat Hepatocyte culture	natural chicoric acid extract (50 and 100 μg/cc)		Insulinotropic Insulin-sensitizing		

Table 3 continued

In vivo	male Wistar rats	aqueous extract (125 mg/kg/day, IP, 21 days)	chicory seed	↓ FBS	anti-diabetic effect	(Pourfarjam et al. 2017)
In vivo	male Wistar rats	aqueous extract (125 mg/kg/day, IP, 28 days)	chicory seed	improvement of insulin sensitivity ↓ insulin resistance	anti-diabetic effect	(Ghamarian et al. 2012)
In vivo	male Wistar rats	Ethanolic extract (250 mg/kg/day, IP, 30 days)	chicory seed	↓ insulin resistance	anti-diabetic effect	(Saad et al. 2024)
In vivo	albino mice (sex indeterminate)	*C.intybus* L powder (10% of the diet) and *C.intybus* L. juice[1], oral, 6 weeks	whole plant	Antioxidant and anti-inflammation	anti-diabetic effect	(Eltokhy et al. 2021)
In vivo	Wistar rats (sex indeterminate)	aqueous extract (250 and 500 mg/kg/day, oral, 3 weeks)	seeds	Antioxidant and anti-inflammation	anti-diabetic effect	(Sharma et al. 2019)
In vivo	Wistar rats (sex indeterminate)	aqueous extract (200 mg/kg/day, oral, 9 weeks)	seeds	Anti-oxidant	anti-diabetic effect	(Chandra et al. 2018)
Clinical	Type 2 diabetes mellitus in female patients	Chicory inulin enriched with oligofructose (10 g/day, oral, two months)	indeterminate	Improving glucose homeostasis	anti-diabetic effect	(Farhangi et al. 2016)

ACC: angiotensin converting enzyme; Hb A1C: Glycated hemoglobin, IP: intraperitoneal. [1] The juice of *C. intybus* L. was prepared by mixing 100 g of fresh *C. intybus* L. with 200 ml of distilled water and left for 48 hours. The mixture was then centrifuged at 2000 rpm for 20 minutes. The supernatant juice was collected and administered to the animals in place of water.

Table 4. anti-obesity effects of chicory and its main constituents based on the type of the extract

Study type		**Extract type**	**Plant part**	**Main mechanism**	**Ultimate effect**	**References**
In vivo	male C57BL/6J mice	chicoric acid (10 and 30 mg/kg/day, oral, four weeks)	from *C. denticulatum* (indeterminate plant part)	↑ AMPK activity ↓ lipogenesis-related gene expression ↑antioxidant enzymes ↓pro-inflammatory cytokines	anti-obesity effects	(Kim et al. 2017)
In vitro	HepG2 hepatocellular carcinoma cells AML-12 murine hepatocyte cells	chicoric acid (20 or 40 μM, 24 hr)				
in vivo	Male C57BL/6 mice	chicoric acid (15 and 30 mg/kg/day, gavage, nine weeks)	indeterminate	↑AMPK activity ↑Nrf2 nuclear translocation ↑antioxidant enzymes ↓pro-inflammatory cytokines	Nonalcoholic Fatty Liver Disease	(Ding et al. 2020)
In vitro	HepG2 cells	chicoric acid (10 and 20 μM, 24 hr)				
in vivo	female C57BL/6J mice	chicoric acid (4 mg/kg, in drinking water, four days) (the exact daily dose indeterminate)	synthetic form	↓ iNOS ↓ TNF-α	hepatic steatosis	(Landmann et al. 2014)
In vitro	Murine RAW264.7 macrophage-like cells	chicoric acid (160 μg/ml, 18 hr)				
In vivo	male C57BL/6J mice	Chicoric acid (15 and 60 mg/kg/day, gavage, eight weeks)	indeterminate	regulating leptin and adiponectin ↓ PPAR γ and C/EBP α ↓ apoptosis anti-oxidant anti-inflammatory	anti-obesity effects	(Xiao et al. 2013)
In vivo	female BALB/c BYj	Aqueous decoction (7 mg of chicory roasted roots/ mouse/day, gavage, 30 days)	Roasted roots	↓ Firmicutes/Bacteroidetes ratio in the feces	anti-obesity effects	(Fouré et al. 2018)
In vitro	murine enteroendocrine STC-1 cell line biochemical test (DPP-IV Inhibition Assay)	Aqueous decoction (0.2, 0.5, and 1% (w/v), 2 hr) 0.87 to 13.89 mg/ml (dry matter)		↑ satiety hormones		
Clinical	Males and females with prediabetes or high-risk factors for prediabetes	Inulin (30 g/day, oral, 18 weeks)	indeterminate	↑GLP-1	anti-obesity effects	(Guess et al. 2015)

AMPK: AMP kinase, C/EBP: CCAAT/enhancer-binding protein; DPP-IV: Dipeptidyl peptidase-4, GLP-1: Glucagon-Like Peptide-1; PPAR: peroxisome proliferator-activated receptor.

Discussion

This narrative review presents evidence on the multi-target therapeutic potential of *Cichorium intybus* (chicory) and its bioactive compounds in managing metabolic syndrome. Chicory not only targets individual symptoms but also improves dyslipidemia, hypertension, hyperglycemia, and obesity.

Dyslipidemia, one of the predisposing factors for developing cardiovascular complications, is mainly characterized by low levels of HDL, elevated levels of low-density lipoprotein (LDL), as well as elevated TG (Jacobsen et al. 2024). Damage to vascular endothelial cells (VEC) plays a crucial role in the initial phases of atherosclerosis, leading to VEC apoptosis and the gradual formation of atheromatous plaques. Also, vascular smooth muscle cells, VECs, as well as foam cells and lipids, have a role in this pathological condition (Choy et al. 2001; Wang and Butany 2017). Herbal remedies for managing and preventing atherosclerosis are gaining attention due to their reduced toxicity and potential to prevent endothelial cell death (Duan et al. 2021; Rameshrad et al. 2018). The development of atherosclerosis is promoted by the increase in ox-LDL and the clustering of vascular cells (Pirillo et al. 2013). Based on the *in vitro* study, the anti-inflammatory properties of chicoric acid involve its ability to counteract oxidative damage associated with atherosclerosis (Tsai et al. 2017).

Acetyl-CoA carboxylase (ACC) enzyme has a significant role in fatty acid synthesis, malonyl-CoA formation, and lipogenesis (Wakil and Abu-Elheiga 2009). HMG-CoA reductase plays a pivotal role in regulating the primary step of cholesterol biosynthesis. The activity of this enzyme is regulated through genetic mechanisms and by negative feedback of cholesterol levels (Gesto et al. 2020). Visfatin, an adipocytokine that promotes inflammation, has paracrine effects on the cardiovascular system (Liu et al. 2009). Inflammatory cytokines increase visfatin expression (Romacho et al. 2013). An animal study showed that chicory supplementation significantly reduced visfatin levels, which could account for chicory's properties in reducing inflammation, preventing atherosclerosis, and acting as an antioxidant. Furthermore, it decreases hepatic and cardiac acetyl-CoA carboxylase activity and HMG-CoA reductase level (Keshk and Noeman 2015).

PXR is a nuclear receptor that regulates detoxification and lipid metabolism. A wide range of exogenous ligands, such as medications, natural extracts, and environmental chemicals, trigger it. It has been demonstrated that hepatic lipogenic genes are induced by PXR activation, leading to liver steatosis (Hakkola et al. 2016). SREBP2 is a transcription factor that regulates the cellular uptake of fatty acids and cholesterol. It is mainly responsible for activating genes involved in cholesterol synthesis. SREBP2 stimulates the expression of genes involved in cholesterol biosynthesis, including mevalonate kinase, HMG-CoA reductase, and synthase (Madison 2016). Through the chaperone protein HSP90, SREBP2 interacts with the nuclear receptor PXR (Karpale et al. 2021; Meng et al. 2024a). Chlorogenic acid promotes the association of PXR with HSP90 while interfering with the interaction between SREBP2 and HSP90, leading to decreased binding stability. As a result, there is a simultaneous decrease in the nuclear accumulation of PXR and SREBP2. Additionally, there was a reduction in the regulation of downstream target genes, such as 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) (Meng et al. 2024a). Based on an animal study, chlorogenic acid has an inhibitory effects in these pathways (Meng et al. 2024a).

More precisely, a critical method for eliminating extra cholesterol from the body is reverse cholesterol transport. ABCA1/G1-dependent cholesterol efflux is a rate-limiting step in reverse cholesterol

transport activity. ABCA1 transports cholesterol to apolipoprotein A1 for HDL formation, and ABCG1 promotes continuous cholesterol efflux to HDL, playing an essential role in its maturation (Yu and Tang 2022). Chicory consumption increased the transcription of ABCA1/G1. Furthermore, it inhibits NADPH oxidase activity (Lin et al. 2015). It should be noted that NADPH activity is responsible for ROS production in macrophages (Drummond et al. 2011).

Hypertension is a global health issue that is on the rise. Based on the last definition, hypertension is defined by systolic blood pressure (SBP) levels equal to or exceeding 130 mmHg and/or diastolic blood pressure (DBP) levels surpassing 80 mmHg in an individual (Bludorn and Railey 2024). In most cases, hypertension serves as a precursor to various conditions in adults, including several heart and kidney impairments (Drozdz and Kawecka-Jaszcz 2014).

Some doses of chicory extracts showed anti-hypertensive (Elgharabawy et al. 2021) or hypotensive effects (Sedighi et al. 2021) due to neutralizing ROS and reducing oxidative stress. This complexity underscores the need for careful consideration of dosage and the potential dual roles of bioactive compounds. While chicory shows promise as a natural remedy for oxidative stress-related conditions, including hypertension and cardiovascular diseases, ongoing research is essential to clarify its mechanisms of action, optimal dosages, and potential side effects.

Insulin resistance, reduced insulin secretion, and hyperglycemia are the defining characteristics of diabetes, which can result in microvascular and macrovascular disorders, as well as severe psychological and physical discomfort in patients (Chatterjee et al. 2017; Mudaliar 2007). Metabolic syndrome and obesity are frequently linked with the development of diabetes (Esser et al. 2014).

Enzymes such as α-amylase and α-glucosidase, which are secreted in saliva and the small intestine, hydrolyze polysaccharides into oligosaccharides and glucose separately (Eichler et al. 1984). These enzymes can be inhibited by anti-diabetic medications, such as acarbose, miglitol, and voglibose, to manage post-meal blood sugar levels (Etxeberria et al. 2012). An *in vitro* study showed *C. intybus* could inhibit α-amylase and α-glucosidase (Attaallah et al. 2021). Furthermore, it exhibits a potential in the suppression of metabolic syndrome by effectively inhibiting lipase and angiotensin-converting enzyme (ACE), *in vitro* assays (Dalar and Konczak 2014).

M1 macrophages have a role in developing insulin resistance (Donath and Shoelson 2011). It has been reported that IL-1β has a role in insulin resistance in type 2 diabetes (Yan et al. 2013). *In vitro, C. intybus* extract, besides decreasing the release of IL-1β, promoted the polarization of macrophages toward the anti-inflammatory M2 phenotype and reduced the accumulation of pro-inflammatory M1 macrophages within white adipose tissue (Shim et al. 2016).

There is a positive relation between protein tyrosine phosphatase 1B activity and insulin resistance and obesity (Calera et al. 2000). Insulin receptor tyrosine kinase activity (Boura-Halfon and Zick 2009) and PI3K activity (Shepherd 2005) are necessary for insulin effects on glucose and lipid metabolism. *C. intybus* extract inhibits protein tyrosine phosphatase 1B activity but increases PI3K levels in adipocytes (Muthusamy et al. 2008).

Obesity is a global health concern with increasing prevalence, associated with numerous diseases, anxiety, and related psychological issues. It is characterized by excessive fat tissue, contributing to low-grade inflammation, oxidative stress, and insulin resistance (Shoelson et al. 2007). Adipose tissue is critical in maintaining lipid homeostasis and energy balance (Rajala and Scherer 2003).

AMPK activation promotes the nuclear translocation of Nrf2, upregulates

antioxidant genes such as SOD and HO-1, while concurrently inhibiting the NF-κB inflammatory pathway. This dual action decreases pro-inflammatory cytokine production, thereby mitigating oxidative stress and inflammation in nonalcoholic fatty liver disease (NAFLD). Chicoric acid dosage supplementations increased p-AMPK and attenuated deteriorative effects of HFD on body weight, weight gain, and body mass index (Ding et al. 2020). Phenolic compounds, including chlorogenic acid from chicory, reduce inflammation, oxidative stress, and hepatic steatosis, exerting strong anti-obesity effects in HFD-fed mice (Cho et al. 2010).

It has been reported that obesity-inducing diets in mice lead to pronounced alterations in the Firmicutes/Bacteroidetes ratio, characterized by a marked increase in the relative abundance of Firmicutes within the distal gut microbiota (Turnbaugh et al. 2008). Similarly, a significantly elevated Firmicutes/Bacteroidetes ratio has also been observed in individuals developing type 1 diabetes (Wen et al. 2008). In agreement with these studies, an animal study showed chicory's prebiotic effects on appetite and gut microbiota composition (Fouré et al. 2018).

C. intybus, a plant with high nutritional value, contains beneficial compounds such as inulin, anthocyanins, phenolic compounds, sesquiterpenes, and caffeic acid derivatives, which have antioxidant and anti-inflammatory properties. Chicoric acid, a naturally occurring phenolic compound in chicory, exhibits its anti-inflammatory and antioxidant properties. Furthermore, it reduces lipogenesis through the activation of AMPK phosphorylation *in vitro*. Chicory exerts beneficial effects for dyslipidemia and obesity through its inhibitory actions on HMG-CoA reductase and visfatin *in vivo*.

Inulin, mainly obtained from chicory roots, has been shown to reduce weight gain *in vivo*. Supplementation with chicory-derived inulin also improved metabolic health, lowered blood glucose in type 2 diabetes patients, and decreased ectopic fat in prediabetic volunteers. These findings highlight the potential of chicory and its inulin as a complementary therapy for metabolic disorders, supporting further clinical investigations.

As an initial step in drug discovery, *in vitro* studies allow us to identify the molecular mechanisms of chicory's effects on four significant aspects of the metabolic syndrome (dyslipidemia and atherosclerosis, hypertension, diabetes, and obesity). Using cell models, these studies enable researchers to closely examine the effects of chicory's active compounds, including inulin, phenolic acids, and sesquiterpene lactones, on signaling pathways associated with insulin resistance, vascular inflammation, and lipid accumulation. For example, *in vitro* studies have shown that chicory extract can be effective in controlling blood sugar and obesity by inhibiting key enzymes such as α-glucosidase and pancreatic lipase. These basic findings are essential for designing animal studies, as they allow us to predict the efficacy and safety of these compounds in more complex physiological models.

In vivo studies using animal models are an essential step in confirming the findings of *in vitro* experiments and are a bridge between basic research and clinical trials. In the case of chicory, studies conducted on animal models with high-fat diet-induced obesity or diabetic mice have shown that consumption of chicory extract can lead to improvements in metabolic parameters, including decreased blood triglycerides, increased HDL-C, decreased systolic blood pressure, and enhanced insulin sensitivity. These studies not only confirm the efficacy of chicory in more complex physiological conditions but also could provide valuable information on the effective dose, potential toxicity, and pharmacokinetics of its active compounds. However, physiological differences between animal models and humans underscore the need for rigorous clinical trials to confirm these findings and determine the appropriate therapeutic dose

for human patients. The results of these preclinical studies provide a solid scientific basis for designing future clinical trials to investigate the effects of chicory on all four components of metabolic syndrome.

A study examining the differences in response to chicory extracts among individuals can help develop tailored dietary guidelines based on genetic and metabolic profiles, leading to more personalized dietary recommendations. Furthermore, studies should be conducted to determine the optimal doses of chicory extracts that maximize hypotensive effects while minimizing the potential for prooxidant effects. The identification and isolation of other bioactive compounds that contribute to the metabolic benefits of chicory also enhance its therapeutic potential by expanding its range of applications. Furthermore, it is crucial to plan research that aims to standardize chicory extracts, thereby ensuring more reliable clinical outcomes through consistent concentrations of bioactive compounds. Research on chicory's effects on various metabolic disorders suggests that there is still much to be investigated regarding these effects. Research in these future directions will provide further insight into chicory's health benefits, and it will also allow researchers to gain a better understanding of how these health benefits can be achieved to optimize its use as a therapeutic agent in clinical settings and as a component of functional food.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Abbreviations

ABCA1-ABCG1: ATP-binding cassette transporters A1 and G1; ACC: Acetyl-CoA carboxylase; ACE: angiotensin converting enzyme; ALT: alanine aminotransferase; AMPK: adenosine monophosphate-activated protein kinase; AST: aspartate aminotransferase; BMI: body mass index; CME: chicory methanolic extract; CME/DT: chicory detannified methanolic extract; CRP: C-reactive protein; DBP: diastolic blood pressure; ET2D: Early stage of type 2 diabetes; GDF-15: Growth differentiation factor 15; GLP-1: glucagon-like peptide-1; GLUT: glucose transporter, GSH: glutathione; GSSG: glutathione disulfide; GTT: glucose tolerance test; HDL-C: high-density lipoprotein cholesterol; HFD: high-fat diet; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; HUVECs: human umbilical vein endothelial cells; IL-: Interleukin-; iNOS: Inducible nitric oxide synthase; IRS: Insulin receptor substrate, LDL: low-density lipoprotein; LT2D: Late-stage of type 2 diabetes; MPMs: mouse peritoneal macrophages; mRNA: messenger RNA; NADPH: Nicotinamide-adenine dinucleotide phosphate; NAFLD: nonalcoholic fatty liver disease; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: Nucleotide-Binding Domain, Leucine-Rich–Containing Family, Pyrin Domain–Containing-3; NO: nitric oxide; ox-LDL: oxidized low-density lipoprotein; PI3K: phosphatidylinositol 3-kinase; PPAR-: peroxisome proliferator-activated receptor -; PXR: pregnane X receptor; ROS: reactive oxygen species; SBP: systolic blood pressure; SOD: superoxide dismutase; SREBP: sterol regulatory element-binding

protein; TG: triglycerides; TNF-α: tumor necrotic factor; VEC: vascular endothelial cells.

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