

REVIEW PAPER

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Biological effects of chicoric acid – the main phenolic compound in chicory (*Cichorium intybus* L.)

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antimicrobial, and antitumor effects have also been reported. Due to these properties, chicoric acid has considerable potential for application in functional foods, nutraceuticals, and pharmaceutical formulations, although its stability and bioavailability remain important limitations.

Keywords: chicoric acid; chicory; biological effects.

INTRODUCTION

Chicory (*Cichorium intybus* L.) is a perennial herbaceous plant belonging to the Asteraceae family, distributed throughout Europe, Western Asia, and North Africa, and today also in many other parts of the world, where it grows both as a wild and cultivated species [1]. Traditionally, it has been used in nutrition – the leaves as a vegetable and the root as a food additive or coffee substitute after roasting [2]. In folk medicine, chicory is known for its beneficial effects on the digestive organs, liver, and bile ducts, and is used as a digestive aid, diuretic, and tonic [1]. Due to the presence of numerous bioactive substances, especially phenolic compounds, interest in the pharmacological effects of chicory has significantly increased in recent decades.

Phenolic compounds represent key carriers of the biological activity of many plants. They are known for a broad spectrum of biological effects – antioxidant, anti-inflammatory, antimicrobial, and cardioprotective [4]. In plants, they play a role in defense against

Abstract

*Chicory (*Cichorium intybus* L.) is a perennial herbaceous plant rich in bioactive compounds, among which chicoric acid is the predominant phenolic constituent found in the leaves and roots. Owing to its structure derived from caffeic and tartaric acids, chicoric acid exhibits strong antioxidant and anti-inflammatory activity. Its biological effects include scavenging reactive oxygen species, activation of the Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, and inhibition of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated inflammatory responses. Chicoric acid also demonstrates immunomodulatory properties through regulation of macrophage and lymphocyte activity. Experimental studies indicate that chicoric acid improves insulin sensitivity, regulates glucose and lipid metabolism, and reduces hepatic fat accumulation via activation of AMP-activated protein kinase. Hepatoprotective,*

antimicrobial, and antitumor effects have also been reported. Due to these properties, chicoric acid has considerable potential for application in functional foods, nutraceuticals, and pharmaceutical formulations, although its stability and bioavailability remain important limitations.

oxidative stress, pathogens, and UV radiation, while in human nutrition they contribute to reducing the risk of chronic diseases associated with oxidative cellular damage [5]. Among them, flavonoids such as kaempferol, quercetin, and luteolin are dominant, acting as potent free radical scavengers, reducing oxidative stress, and potentially protecting cell membranes from damage [6]. In addition to flavonoids, chicory also contains sesquiterpene lactones (e.g., lactucin, lactucopicrin, and 8-deoxylactucin), responsible for the characteristic bitterness of the plant and exhibiting anti-inflammatory, antimicrobial, and hepatoprotective properties [7].

A particularly important component of chicory is inulin, a fructopolysaccharide that accumulates in the root of the plant. Inulin exerts prebiotic effects, stimulates the growth of beneficial bacteria in the gut microbiota, and contributes to improved glucose metabolism and lipid profile [8].

As many as 64 phenolic acids and flavonoids have been isolated from several varieties of *Cichorium inty-*

bus [9]. Phenolic acids that occupy a significant place include chicoric, caffeic, chlorogenic, and ferulic acids. Among them, chicoric acid is especially prominent and has been identified as the dominant phenolic constituent in the leaves and roots of the plant [10]. Chicoric acid belongs to the group of hydroxycinnamic acid derivatives and is known for its potent antioxidant and immunomodulatory activity [1].

Data on the content of chicoric acid in *C. intybus* vary considerably, particularly depending on the plant part analyzed. The average concentration of chicoric acid in the aerial parts (herb) of *C. intybus* is 2.74 mg/g dry weight, whereas in the root it is 0.32 mg/g dry weight when extraction is performed with methanol. It should also be noted that chicoric acid is the most abundant phenolic compound in chicory herb [6]. The presence of chicoric acid in high concentrations suggests that this molecule may be the main carrier of chicory's biological activity. Considering the traditional use of the plant, its biochemical composition, and scientific evidence regarding the biological efficacy of chicoric acid, it is justified to investigate and thoroughly analyze the biological effects of this compound [11].

CHEMICAL NATURE OF CHICORIC ACID

Chicoric acid is a phenolic compound known for its strong antioxidant activity. Chemically, it is a derivative of caffeic and tartaric acids and is most commonly described as dicaffeoyl-tartaric acid, meaning that two molecules of caffeic acid are esterified on the tartaric acid backbone. Its molecular formula is $C_{22}H_{18}O_{12}$, and the molecule contains two catechol (3,4-dihydroxyphenylpropenoic) fragments connected through a tartaric backbone (Figure 1) [12,13].

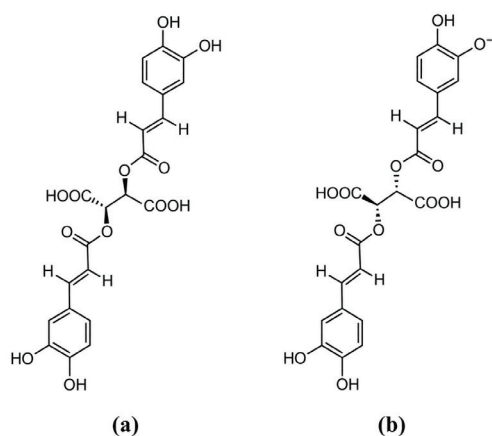


Figure 1. Chemical structure of D-chicoric acid (a) and biologically active L-chicoric acid (b) [14].

A key structural feature of chicoric acid is the presence of two caffeoyl groups with an ortho-dihydroxy (catechol) arrangement on the aromatic rings. Such a

configuration enables efficient hydrogen or electron donation to free radicals and stabilization of the resulting phenoxyl radical through resonance delocalization [15]. This mechanism explains the ability of chicoric acid to scavenge reactive oxygen species (ROS) and interrupt chain oxidation reactions involving lipids, proteins, and nucleic acids [13].

The connection with tartaric acid further affects the stability and electronic distribution of the molecule. The tartaric skeleton enables the simultaneous presence of two phenolic units in close proximity, increasing overall polarity and the possibility of intramolecular hydrogen bonding. This facilitates electron delocalization and regeneration of the phenolic form after radical neutralization [16]. The synergy between the two caffeoyl groups explains why chicoric acid demonstrates stronger antioxidant effects than monomeric caffeic acid derivatives in many assays.

In experimental models, including the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, chicoric acid demonstrated a high capacity for free radical neutralization and protection of biological macromolecules from oxidative damage [17]. In addition to direct radical scavenging, it has also been shown to affect cellular signaling pathways by increasing the activity of antioxidant defense enzymes and reducing oxidative stress [15].

BIOLOGICAL ACTIVITY OF CHICORIC ACID

Chicoric acid is a natural polyphenol that, owing to its structure, exhibits not only exceptionally strong antioxidant activity but also a broad spectrum of beneficial biological effects. Its activity includes antioxidant, anti-inflammatory, immunomodulatory, and metabolic mechanisms confirmed in numerous *in vitro* and *in vivo* studies [13,18,19].

ANTIOXIDANT ACTIVITY

The antioxidant activity of chicoric acid is reflected in its ability to scavenge free radicals and regenerate endogenous antioxidant enzymes. In the previously mentioned DPPH assay, as well as in the ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate)) and Ferric Reducing Antioxidant Power (FRAP) assays, chicoric acid showed a high capacity for radical neutralization, attributed to the synergy of the two caffeoyl groups, which enables more efficient electron transfer and stabilization of radical intermediates [15,18]. In a cellular model of oxidative stress in HepG2 cells, chicoric acid activates the Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, increases the expression of heme oxygenase-1 (HO-1), and reduces the accumulation of reactive oxygen species [19]. Furthermore, it has been demonstrated that these reduced ROS levels indirectly increase the function of superoxide dis-

mutase (SOD) and catalase, enhance nitric oxide (NO) bioavailability, and maintain mitochondrial membrane potential, thereby preventing proapoptotic responses in endothelial cells treated with oxidized low-density lipoprotein (LDL) particles [20]. Based on its antioxidant and anti-inflammatory activity, the beneficial effect of chicoric acid in lipopolysaccharide-induced acute lung injury has also been experimentally confirmed [21].

ANTI-INFLAMMATORY ACTIVITY

Chicoric acid exhibits pronounced anti-inflammatory potential through inhibition of pro-inflammatory signaling pathways. It has been shown to block activation of the nuclear factor NF-κB pathway by reducing phosphorylation of the inhibitory protein IκBα, thereby decreasing NF-κB translocation into the nucleus. Consequently, the expression of cyclooxygenase-2 and inducible nitric oxide synthase is reduced [13,22]. This inhibition leads to decreased production of inflammatory cytokines, including TNF-α, IL-1β, and IL-6, and prevents cell damage caused by chronic inflammation [22,23]. In models of colitis and endometritis, chicoric acid reduced inflammatory lesions and inhibited myeloperoxidase and cytokine production, partly through activation of the Nrf2/HO-1 pathway and inhibition of ferroptosis [19].

IMMUNOMODULATORY ACTIVITY

Chicoric acid affects the functional activity of immune cells. In macrophages, it modulates the synthesis of nitric oxide and pro-inflammatory cytokines, while in lymphocytes it can regulate proliferation and expres-

sion of surface receptors associated with signaling and antigen recognition [25,26]. For example, under conditions of long-term stress, administration of chicoric acid supported an increase in CD4⁺ and CD8⁺ T-cell populations, increased expression of the co-stimulatory molecules CD28 and CD80, and reduced CTLA-4 expression, along with increased IL-12, IFN-γ, and IL-2 levels and decreased IL-10, thereby contributing to restoration of the Th1/Th2 balance [26].

METABOLIC AND HEPATOPROTECTIVE EFFECTS

Numerous studies indicate that plant-derived polyphenols play an important role in the prevention and treatment of hepatic steatosis and lipid metabolism disorders [27]. Chicoric acid exhibits significant metabolic effects. In experimental models of diabetes and metabolic syndrome, chicoric acid increases insulin sensitivity, improves glucose utilization, and normalizes lipid profiles [18,28]. The mechanism includes activation of the AMP-activated protein kinase (AMPK) signaling pathway, inhibition of lipogenesis, stimulation of fatty acid oxidation, and enhancement of mitochondrial function (Figure 2) [15,19,28].

In mouse models fed a high-fat diet, oral administration of chicoric acid reduced body weight, plasma total cholesterol and triglyceride concentrations, and alleviated hepatic steatosis [23]. This effect is associated with activation of the AMPK pathway and suppression of SREBP-1c/ACC signaling [29]. Through AMPK activation, chicoric acid induces phosphorylation of ACC, thereby inactivating it and reducing malonyl-CoA levels, ultimately decreasing *de novo* lipogenesis [15,30]. Chicoric acid also increases expression of β-oxidation

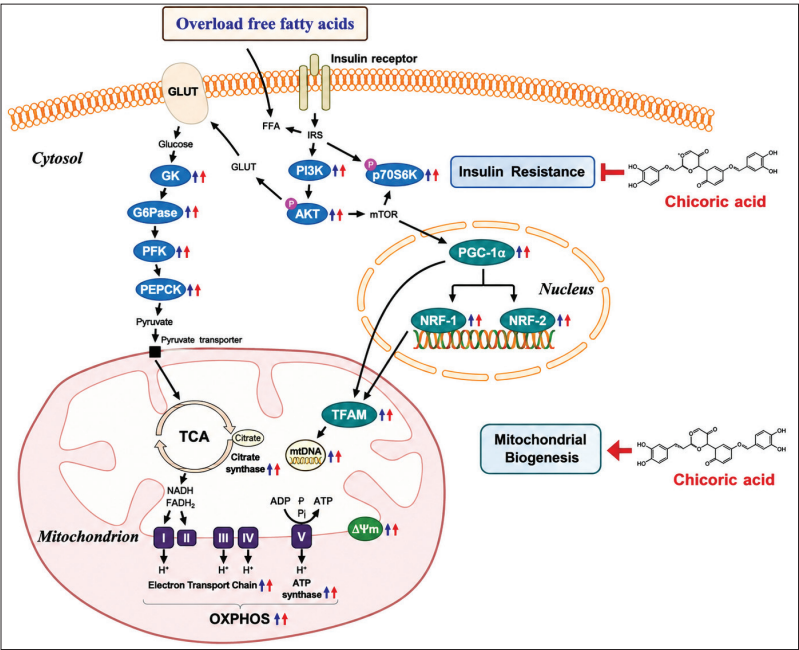


Figure 2. Mechanisms of chicoric acid action in metabolic syndrome and diabetes [28].

markers and decreases HMG-CoA reductase activity in the liver, contributing to improved lipid profiles (**Figure 3**) [28].

In addition, chicoric acid demonstrates hepatoprotective activity by reducing steatosis and oxidative damage in hepatocytes, thereby preserving liver functional capacity [28]. In models of nonalcoholic fatty liver disease, chicoric acid significantly reduced steatosis, tissue damage, and alanine and aspartate aminotransferase levels in animals fed a high-fat diet [28]. In methotrexate-induced hepatotoxicity models, chicoric acid reduced lipid peroxidation, increased Nrf2/HO-1 expression, and normalized alanine transaminase (ALT) and aspartate transaminase (AST) levels, confirming protection of hepatocytes against cytotoxic damage [31].

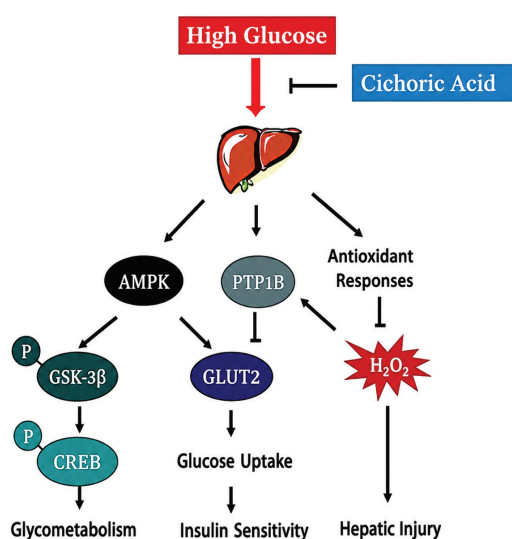


Figure 3. Scheme of the metabolic and hepatoprotective effects of chicoric acid [22].

ANTIMICROBIAL ACTIVITY

Chicoric acid demonstrates significant antimicrobial potential against bacteria, viruses, and fungi. In bacterial models, metal complexes of chicoric acid with cobalt, copper, nickel, and zinc have been tested against strains such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Proteus vulgaris*, as well as the fungus *Candida albicans* (**Figure 4**). These complexes exhibit selective bacteriostatic and fungicidal effects attributed to destabilization of bacterial and fungal membranes and disruption of cellular metabolism. Free chicoric acid also exerts bacteriostatic effects, although less potently [32].

Additionally, chicoric acid inhibits bacterial protein tyrosine phosphatase YopH from *Yersinia enterocolitica*, suggesting interference with signaling pathways associated with pathogen virulence. This mechanism represents a specific inhibition of a bacterial virulence factor, reducing bacterial phagocytosis into host cells [34].

In viral models, chicoric acid was investigated in hepatitis B infection cell models (HepG2.2.15 cells), where concentrations of 10–100 µg/mL reduced viral production, primarily HBsAg and HBeAg, and inhibited viral DNA replication [35]. Recent studies also suggest that chicoric acid may directly interfere with SARS-CoV-2 by binding to the viral nucleocapsid protein, disrupting its interaction with viral RNA and reducing viral replication in cell cultures [36]. Chicoric acid has also demonstrated inhibition of HIV-1 integrase and prevention of HIV DNA integration under in vitro conditions [37].

ANTITUMOR ACTIVITY

Chicoric acid exhibits potential antitumor activity in various *in vitro* models, affecting proliferation, survival, and cell death mechanisms in tumor cells. In gastric

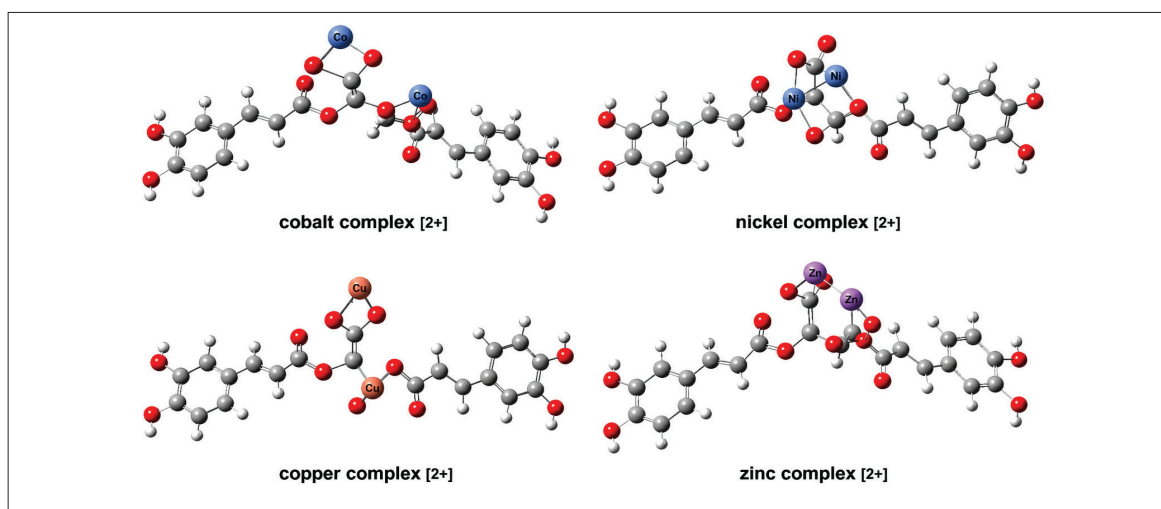


Figure 4. Proposed structure of metal complexes with chicoric acid [33].

cancer cells, chicoric acid induces autophagy through activation of the endoplasmic reticulum stress response and the AMPK signaling pathway, resulting in inhibition of tumor cell growth [39]. Similarly, in colorectal cancer cells, chicoric acid showed antiproliferative and proapoptotic effects associated with inhibition of CDC25 phosphatase and disruption of cell cycle regulation [40]. Previously described metal complexes of chicoric acid also demonstrated cytotoxicity against different tumor cell lines [32].

In addition to studies involving the pure compound, cytotoxic potential has also been confirmed in chicory extracts rich in chicoric acid, which reduced tumor cell viability in various experimental systems [41]. Although these findings indicate promising antitumor potential, most available data originate from *in vitro* studies, and additional *in vivo* investigations are necessary to confirm these effects.

APPLICATIONS AND POTENTIAL OF CHICORIC ACID IN PHARMACY AND NUTRITION

As a component of functional foods, chicoric acid from different chicory varieties is used because of its ability to reduce oxidative stress and inflammation, thereby enriching the nutritional profile of products intended for the prevention of chronic diseases. In nutraceuticals, it is particularly interesting because it has been shown to modulate glucose and lipid metabolism, potentially contributing to body weight regulation and improved insulin sensitivity [42,43]. Plant extracts rich in chicoric acid are increasingly incorporated into standardized supplement formulations due to their consistent antioxidant and anti-inflammatory effects [13].

Furthermore, as a natural preservative in food formulations, chicoric acid has demonstrated the ability to inhibit lipid oxidation in oils and slow the growth of certain pathogenic bacteria, thereby contributing to prolonged shelf life of food products. One study showed that 0.02% and 0.05% concentrations of chicoric acid significantly slowed oil peroxidation compared with the control group over several days [44].

LIMITATIONS AND CHALLENGES RELATED TO STABILITY AND BIOAVAILABILITY

Challenges related to the stability and bioavailability of caffeic acid derivatives significantly limit their application. These compounds are sensitive to temperature, light, and pH conditions encountered during food and pharmaceutical production, which may result in degradation and loss of activity [45]. In addition, low water solubility and intensive presystemic metabolism (first-pass metabolism) reduce the amount reaching target tissues, compromising the effectiveness of oral administration [46].

To overcome these limitations, nano- and microencapsulation techniques such as liposomes, nanogels, and polymeric nanocapsules have been developed to protect the active compound, improve release and absorption, and enable targeted delivery [47]. In addition to encapsulation, improved absorption of chicoric acid has also been achieved by the addition of natural polymers such as chitosan [48]. Metabolic engineering aimed at increasing the content of polyphenolic compounds in foods is also being considered as an approach to overcoming some of these challenges [49].

CONCLUSIONS

Chicoric acid represents one of the most important bioactive phenolic constituents of chicory, with a broad spectrum of beneficial biological effects confirming its therapeutic and nutritional potential. Its strong antioxidant, anti-inflammatory, immunomodulatory, and metabolic activities suggest that it could play an important role in the prevention and supportive treatment of metabolic disorders, inflammatory diseases, viral infections, and certain forms of cancer.

In addition, its application in functional foods, nutraceuticals, and potentially as a natural preservative further emphasizes its value in the food and pharmaceutical industries. However, limited stability and bioavailability remain major challenges. Future research should focus on the development of advanced nanoformulations, clinical validation of pharmacological effects, and evaluation of long-term safety and interactions with other bioactive compounds.

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Biološki efekti cikorinske kiseline – glavnog fenolnog jedinjenja u cikoriji (*Cichorium intybus* L.)

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Kratak sadržaj

Cikorija (Cichorium intybus L.) je višegodišnja zeljasta biljka bogata bioaktivnim jedinjenjima, među kojima je cikorinska kiselina dominantno fenolno jedinjenje prisutno u listovima i korenu. Zahvaljujući svojoj strukturi izvedenoj iz kafene i vinske kiseline, cikorinska kiselina ispoljava izra-

ženu antioksidativnu i antiinflamatornu aktivnost. Njeni biološki efekti uključuju uklanjanje reaktivnih kiseoničnih vrsta, aktivaciju signalnog puta Nrf2 (eng. Nuclear factor erythroid 2-related factor 2) i inhibiciju inflamatornih odgovora posredovanih NF-κB (eng. Nuclear factor kappa-light-chain-enhancer of activated B cells) signalnim putem. Cikorinska kiselina takođe pokazuje imunomodulatorna svojstva regulacijom aktivnosti makrofaga i limfocita. Eksperimentalne studije ukazuju da cikorinska kiselina poboljšava osetljivost ćelija na insulin, reguliše metabolizam glukoze i lipida i smanjuje nakupljanje masti u jetri aktivacijom AMP-aktivirane protein kinaze. Takođe su zabeleženi hepatoprotektivni, antimikrobni i antitumorski efekti. Zbog navedenih svojstava, cikorinska kiselina ima značajan potencijal za primenu u funkcionalnoj hrani, nutraceuticima i farmaceutskim formulacijama, iako i dalje postoje ograničenja po pitanju njene stabilnosti i biodostupnosti.

Ključne reči: cikorinska kiselina; cikorija; biološki efekti.