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REVIEW

The Bioactive Effects of Chicoric Acid As a Functional Food Ingredient

Ye Peng,[1,2] Quancai Sun,[1] and Yeonhwa Park[2]

[1]*School of Food and Biological Engineering, Jiangsu University, Zhenjiang, China.*
[2]*Department of Food Science, University of Massachusetts, Amherst, Massachusetts, USA.*

ABSTRACT Chicoric acid, a hydroxycinnamic acid, has been reported to possess a variety of health benefits, including antivirus, antioxidant, anti-inflammation, obesity prevention, and neuroprotection effects. The purpose of this article is to summarize current knowledge of pharmacological and biological effects of chicoric acid. Since most studies to date on chicoric acid have limited their focus to cell cultures and animals, more human and mechanistic studies are therefore needed to further determine the beneficial effects of chicoric acid as a potential functional food ingredient.

KEYWORDS: • *chicoric acid* • *chicory* • *food bioactive* • *purple coneflower*

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INTRODUCTION

Hydroxycinnamic acids have been used as medications and/or nutraceuticals to promote health based on their antioxidative, anti-inflammatory, antiviral, and immune-stimulating properties.[1,2] Chicoric acid, a hydroxycinnamic acid that is a member of the phenylpropanoid family, contains two caffeoyl units.[2] Chicoric acid mainly presents in two forms: first, the most abundant natural form of chicoric acid is L-chicoric acid (Fig. 1); and second, the acid presents in stereoisomer meso-chicoric acid [*i.e.*, dicaffeoyl-meso-tartaric acid or di-E-caffeoyl-(2*R*-3*S*)-(−)-tartaric acid)].[3]

Chicoric acid is present in roots of a large number of plants (63 genera and species), including many plants grown in the Mediterranean area,[3] and many of these plants have been consumed as alternative medicines or food supplements for some time.[2,4] Because chicoric acid is found in especially high amounts in chicory (*Cichorium intybus*), purple coneflower (*Echinacea purpurea*), and basil, the acid is often used as a marker for quality check of herbal products from these plants.[5] The roots of chicory and purple coneflower are usually baked, grounded, and used as a coffee substitute in Europe.[6] In Turkey, an herbal tea made from chicory has been used historically for treatment of diabetes, epilepsy, hemorrhoids, inflammation, and digestive disorders.[7] Plant roots containing chicoric acid have been used in Asian traditional medicine as a tonic for curing infectious diseases, inflammatory diseases, eye diseases, and nerve injuries.[7,8] Commercial products made from purple coneflower are currently popular alternative medicines widely used in North America for cold and flu prevention.[9] More recently, an increasing number of publications have reported the beneficial effects of chicoric acid in cell culture and animal studies. This review summarizes these health benefit studies and the underlying mechanisms of chicoric acid.

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Address correspondence to: Quancai Sun, PhD, School of Food and Biological Engineering, Jiangsu University, Zhenjiang 212001, China, E-mail: sqctp8@ujs.edu.cn *or Yeonhwa Park, PhD, Department of Food Science, University of Massachusetts, 102 Holdsworth Way, Amherst, MA 01003, USA, E-mail:* ypark@foodsci.umass.edu

DATABASE AND LITERATURE SEARCH STRATEGIES

In this literature review, the PubMed and Web of Science databases were searched using the keywords ''chicoric acid'' and its alias ''cichoric acid.'' Data were collected from 1996 to December 2017. Articles found from these sources were evaluated for relevancy. Duplicates and unrelated results, such as publications about extraction and purification of chicoric acid, were excluded. A total of 75 articles were selected and their full texts were reviewed, followed by an evaluation of the bibliographies of relevant articles. Among the 75 articles, 45 studied beneficial health effects of chicoric acid in cell or animal models. These are summarized in Tables 1 and 2. The other relevant publications are cited in context below.

BIOLOGICAL EFFECTS OF CHICORIC ACID

The main benefits of chicoric acid include antivirus, anti-inflammation, glucose and lipid homeostasis, neuroprotection, and antioxidation effects. Biological activities and related mechanisms of chicoric acid from *in vitro* and *in vivo* studies are summarized in Tables 1 and 2.

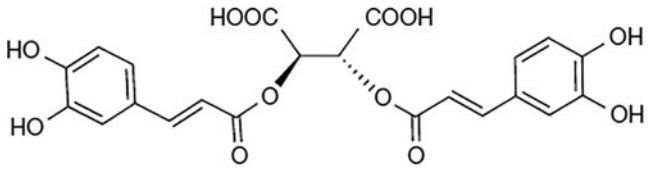

FIG. 1. Molecular structure of L-chicoric acid. The most abundant natural form of chicoric acid is L-chicoric acid, that is, (-)-chicoric acid, 2,3-dicaffeoyl-L-tartaric acid, 2,3-*O*-dicaffeoyltartaric acid, 2*R*,3*R*-*O*-dicaffeoyltartaric acid, or di-E-caffeoyl-(2*R*-3*R*)–(-)-tartaric acid.

ANTIVIRAL EFFECTS OF CHICORIC ACID

The first reported bioactive effect of chicoric acid is its ability to inhibit infection with human immunodeficiency virus 1 (HIV-1).[10] Several studies reported that chicoric acid inhibits infection with HIV-1 by deactivating HIV-1 integrase.[10–17] HIV-1 integrase is a multidomain enzyme required for integration of viral DNA into the host genome, a critical step in viral replication.[18] Inhibition of HIV-1 integration by chicoric acid results in stopping virus replication, leading to increased T-lymphoblastoid cell viability.[11–13,15,16]

It has been further suggested that chicoric acid decreases integrase binding site activity, including downregulation of HIV 3′-end processing products,[10] occupation of HIV-1 integrase catalytic core,[14] chelation of integrase divalent cations,[11] increase of long terminal repeat circle formation,[15] and inhibition of integrase-mediated catalysis.[12] Hu *et al.*[19] reported that mutation of HIV integrase might result in blocking of chicoric acid-specific binding sites, and King *et al.*[20] further reported that the mutation on glycine to serine at position 140 (G140S) of HIV integrase reduced chicoric acid's effects on HIV infection, suggesting that the integrase G140S might be a target site of chicoric acid.

There are a few studies that are using new computational techniques, including molecular docking and quantitative structure–activity relationship (QSAR) analysis, to identify the binding sites of chicoric acid with HIV-1 integrase.[19,21,22] Chicoric acid binds HIV-1 integrase at its two arms, including the s-cis/s-cis isomer and s-cis/s-trans isomer arrangements.[21] Based on the observation that the s-cis/s-cis isomer exhibits the most stable binding, this site was suggested to be the target of chicoric acid to inhibit HIV integrase. Another study using QSAR analysis indicated that polyaromatic rings of chicoric acid are central linkers in binding to HIV-1 integrase.[22] In addition to integrase, reverse transcriptase is another potential target of chicoric acid[17,23] as chicoric acid downregulates reverse transcriptase of HIV-1 through inhibition of the transactivator of transcription, an important protein promoting HIV-1 reverse transcription.[23]

Although chicoric acid may be a potential treatment for HIV, there are several limitations of using naturally occurring chicoric acid as a treatment, such as poor stability and limited cell permeability due to diacid moiety.[24] To overcome these limitations, chicoric acid analogs have been introduced, such as an analog of a decarboxyl compound, while extending a caffeoyl group on 3,4,5-trihydroxycinnamoyl sidechains, which showed improved stability and cell bioavailability.[24–26] This analog also exhibited high potency against HIV integrase infectivity.[24–26]

CHICORIC ACID AND INFLAMMATORY RESPONSES

Chicoric acid has been found to ameliorate inflammation induced by lipopolysaccharides (LPSs) in both cell culture and mice. Reduced inflammation was associated with downregulation of nuclear factor κB (NF-κB) and tumor necrosis factor α (TNF-α),[27–30] which are two major regulators of inflammation responses.[31–33] Several other proinflammatory factors, including nitric oxide synthase, cyclooxygenase-2 (COX-2), prostaglandin E_2, interleukin-1β (IL-1β), IL-12, and IL-18, have also been reported to be downregulated by chicoric acid.[27,29,34–37]

However, two relevant studies showed results inconsistent with the above. Matthias *et al.*[38] reported that LPSs inhibited NF-κB expression, which was reversed by chicoric acid treatments in Jurkat E6.1 leukemia T cell lymphoblasts. The other reported that echinacea extracts (containing chicoric acid) upregulated LPS-induced TNF-α in rat alveolar macrophages.[39] Inconsistencies may be due to dosage and types of LPSs used (i.e., 0.1 vs. 1 μg/mL)[28,37,40–42] and/or other components present in treatments.[30,43] Overall, since the proinflammatory factors above are related to the occurrence of many chronic diseases, most research suggests that chicoric acid may be considered a preventive tool for inflammation-associated diseases[27,29,34–37]; however, further evaluation is needed.

CHICORIC ACID AND GLUCOSE METABOLISM

Chicoric acid has been reported to promote glucose uptake in muscle cells and hepatocytes through activating the insulin receptor substrate/phosphoinositide 3-kinase/protein kinase B (Akt) pathway.[44–47] Zhu *et al.*[47,48] suggested that chicoric acid activated Akt through the AMP-activated protein kinase α (AMPKα)-dependent mechanism, which is a master regulator for energy homeostasis and also plays a key role in glucose metabolism. However, the mechanism underlying how chicoric acid induces AMPKα activation is not currently known.

In addition to AMPKα, glucosidase, a digestive enzyme for carbohydrates, was reported to be suppressed by chicory,[49] which can contribute to reduced glucose levels.[50,51] Another enzyme, protein tyrosine phosphatase 1B (PTP1B), negatively regulates the insulin signaling pathway by inhibiting the activity of insulin receptor kinase.[52] Two studies with molecular docking showed molecular interactions between the allosteric site of PTP1B and chicoric acid, which suggests that chicoric acid might inhibit PTP1B and further activate the insulin signaling pathway.[53,54]

In *in vivo* studies, chicoric acid (or leafy extracts of echinacea or basil) reduced streptozotocin induced-hyperglycemia in mice.[44,48,55,56] In these studies, protection of pancreatic β-cells by chicoric acid was attributed to its

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Table 1. *In Vitro* Effects of Chicoric Acid in the Treatment of Various Disorders

Disorders	*Models*	*Dose (μM)*	*Duration (h)*	*Effects*	*Suggested mechanisms*	*References*
Antiviral effects	H9 and MT-2 human T-lymphoblastoid	1.05–10.5	48	↑ Infected cell viability; ↓ HIV-1 integrase activity	↓ HIV 3′-end processing products	10
	H9 and MT-2 human T-lymphoblastoid	0.4	48	↓ HIV-1 integrase activity	↓ HIV integrase catalytic core	14
	MT-2 human T-lymphoblastoid	105	48	↓ HIV-1 reverse transcriptase activity	↓ HIV-1 envelope glycoprotein 120	23
	MT-2 human T-lymphoblastoid	0.4	72	↑ Infected cell viability; ↓ HIV-1 reverse transcriptase activity; ↓ HIV-1 reverse transcriptase release	N/A	17
	MT-2 human T-lymphoblastoid	25	72	↓ HIV-1 integrase replication	N/A	13
	MAGI human cervical epithelial carcinoma	100	52	↓ HIV-1 integrase activity	↓ HIV-1 Tat protein synthesis	78
	H9 and MT-2 human T-lymphoblastoid	0.1–10	24	↓ Viral replication; ↓ HIV-1 integrase activity	↑ Integrase divalent cation chelation	11
	MT-4 human T-lymphoblastoid	70	2	↓ Viral replication cycle; ↓ viral entry	↓ HIV-1 envelope glycoprotein 120	81
	MT-2 human T-lymphoblastoid	4.2	72	↑ Infected cell viability; ↓ HIV-1 integrase activity	↑ Long terminal repeat circle formation	15
	H9 and MT-2 human T-lymphoblastoid	50	1–4	↓ HIV-1 integrase activity	↓ Integrase binding site activity	16
	H9 and MT-2 human T-lymphoblastoid	25	1	↓ HIV-1 integrase activity	↓ Integrase-mediated catalysis	12
Glucose metabolism	L6 rat myotubes and insulinoma-derived ISN-1 pancreatic β-cells	200 and 20–100	1–2	↑ Glucose uptake; ↑ insulin secretion	N/A	46
	INS-1 pancreatic β-cells; L6 myotubes; isolated hepatocytes (rat)	105–210	1–3	↑ Glucose uptake; ↑ insulin secretion	N/A	44
	HepG2 human hepatoma	100	24	↓ Insulin resistance; ↓ NO and ROS	↑ GLUT2 translocation; ↑ Akt; ↓ MAPK; ↓ NF-κB	47
	HepG2 human hepatoma	100	24	↑ Glucose uptake	↑ IRS-1; ↑ Akt; ↑ AMPα; ↑ SIRT1; ↑ GSK-3β; ↓ CREB	48
Inflammation responses	RAW 264.7 mouse macrophage	4.2	4	N/A	↓ NF-κB; ↓ TNF-α	30
	Macrophage	N/A	N/A	↓ Cell inflammation	↓ TNF-α	29
	Jurkat E6.1 human leukemic T cell lymphoblast	17	4	N/A	↑ NFκB	38
	Mouse peripheral blood mononuclear cells	0.5–4.2	4	↑ Immune homeostasis	↑ IL-2; ↑ IFN-γ; ↓ IL-4	35
	BV-2 mouse microglia	80	4	↓ Cell inflammation	↓ iNOS; ↓ COX-2; ↓ PGE2; ↓ IL-1β; ↓ TNF-α	27
	Human umbilical vein endothelial cells	12.5–100	24	↓ Endothelial dysfunction; ↓ cell apoptosis; ↑ cell viability; ↓ ROS	↑ SOD; ↑ eNOS; ↓ Bax/Bcl-2; ↓ cleaved caspase-3; ↓ MAPK; ↓ NF-κB	36
	HT-29 human colorectal adenocarcinoma	42	12	↓ Cell inflammation	↓ NF-κB; ↓ COX-2; ↓ IL-1β; ↓ IL-18	37
Oxidative stress	Human plasma	1	5	↓ Cu(II)-catalyzed LDL oxidation	N/A	72
	RAW264.7 mouse macrophage	16–32	20	↓ Oxidative stress	↓ PGE2; ↓ TNF-α; ↓ IL-1β; ↓ NF-κB; ↓ Akt	41
	RAW264.7 mouse macrophage	N/A	20	↓ Oxidative stress and ↓ NO	↑ GSH; ↓ iNOS; ↓ NF-κB	42
	L6 rat myotubes	5–50	1	↓ ROS	↑ GPx; ↑ SOD; ↑ p-AMPKα; ↑ PGC-1α	68
	RGC-5 rat retinal ganglion cells	0.025	24	↑ Cell viability and ↓ ROS	↓ Cleaved PARP; ↓ cleaved caspase-3	1
	RAW264.7 mouse macrophage	340	19	↓ Oxidative stress	↓ MyD88; ↓ iNOS; ↓ TNF-α	61
	HepG2 human hepatoma	100	24	↓ NO; ↓ ROS	↓COX-2; ↓iNOS; ↓ NF-κB	47
	Daudi and Namalwa B lymphocyte; JeKo-1 mantle cell lymphoma, THP-1 monocytes, and HepG2 hepatoma (human)	21–105	12–48	↓ B cell-activating factor belonging to the TNF family (BAFF)	↓ NF-κB; ↓ IκB	71
	BV-2 mouse microglia	80	4	↓ Oxidative stress	↓ NF-κB; ↓ MAPK; ↑ Nrf2	28
	SH-SY5Y human neuroblastoma	50	24	↓ Oxidative stress; ↑ cell viability	↑ Nrf2; ↑ HO-1; ↑ NQO-1; ↑ CAT; ↑ GSH; ↓ TNF-α; ↓ IL-1β; ↓ malondialdehyde	70
Others	HL-7702 human hepatocytes and HepG2 human hepatoma	20–200	48	↑ Infected cell viability; ↓ HBV activity	↓ HBV surface and envelope antigen	82
	Caco-2 and HCT-116 epithelial colorectal adenocarcinoma (human)	105–315	24–48	↓ Cell proliferation; ↑ cell apoptosis; ↓ telomerase activity	↑ DNA fragmentation; ↑ cleaved caspase-9; ↑ cleaved PARP	75
	HeLa cervical carcinoma and MCF-7 breast carcinoma (human)	0.05	24	↓ Doxorubicin-induced cell death	N/A	83
	Human skin fibroblasts	2	24	↓ Dermal fibroblast senescence	↓ MMP-3	76
	3T3-L1 mouse preadipocytes	100	48	↑ Cell apoptosis and ↓ mitochondrial membrane potential	↑ Cleaved caspase-3; ↓ Akt; ↑ MAPK; ↓ JNK and ERK1/2	60
	3T3-L1 mouse preadipocytes	100	24	↑ Free radical scavenging	N/A	84

↑, increase; ↓, decrease; N/A, not available; Akt, protein kinase B; AMPKα, AMP-activated protein kinase α; Bax/Bcl-2, B cell lymphoma 2-associated X/B cell lymphoma 2; BSO, 1-buthionine-(S,R)-sulfoximine; CREB, cAMP response element-binding protein; CAT, chloramphenicol acetyl transferase; COX-2, cyclooxygenase-2; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular signal-regulated kinase 1/2; GLUT2, glucose transporter 2; GPx, glutathione peroxidase; GSH, glutathione; GSK-3β, glycogen synthase kinase 3β; HBV, hepatitis B virus; HIV-1, human immunodeficiency virus 1; 4-HNE protein adducts, 4-hydroxynonenal protein adducts; HO-1, heme oxygenase; IFN-γ, interferon γ; IκB, inhibitor of kappa B; IL-1β, interleukin 1 beta; iNOS, nitric oxide synthase; IRS-1, insulin receptor substrate 1; JNK, c-Jun N-terminal kinase; LPSs, lipopolysaccharides; MAGI, HeLa CD4+ HIV-1 LTR-β-gal cells; MAPK, mitogen-activated protein kinase; MMP-3, matrix metalloproteinase-3; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor κB; NQO-1, NAD(P)H dehydrogenase; Nrf2, nuclear factor erythroid 2-related factor 2; LDL, low-density lipoprotein; PARP, poly-(ADP-ribose) polymerase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator α; PGE2, prostaglandin E2; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; Tat, transactivator of transcription; TNF-α, tumor necrosis factor α.

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Table 2. *In Vivo* Effects of Chicoric Acid in the Treatment of Various Disorders

Diseases	*Species (sex)*	*Models*	*Dose (mg/kg/d)*	*Duration (days)*	*Effects*	*Suggested mechanisms*	*References*
Brain function	Swiss albino mice (M)	Restraint stress (Porsolt's swim stress and conical polypropylene tubes)	1–2 p.o.	14	↓ Behavioral despair; ↑ learning ability; ↑ neurotransmitters	↑ Norepinephrine ↑ dopamine; ↑ 5-hydroxytryptamine	62
	Sprague-Dawley rats and ICR mice (M)	Retinal damage (*N*-methyl-D-aspartate/ optic nerve crush)	2 μg/eye intravitreal injection	7	↑ Retinal ganglion cell viability	↓ Cleaved PARP; ↓ cleaved caspase-3	1
	C57BL/6J mice (M)	LPS challenges	0.5 g/L drinking water	45	↓ Memory impairment; ↓ amyloidogenesis	↓ Amyloid β ($A\beta_{1-42}$); ↓ BACE1; ↓ MAPK; ↓ NF-κB	27
	C57BL/6J mice (M)	LPS challenges	0.5 g/L drinking water	45	↓ Oxidative stress-induced neuron damage	↓ MAPK; ↓ NF-κB; ↓ iNOS; ↓ IL-1β; ↓ TNF-α; ↑ Nrf2; ↑ HO-1; ↑ NQO-1	28
	C57BL/6J mice (M)	D-galactose challenges	100 i.p.	56	↓ Neuron damage; ↓ hippocampus shrinkage	↓ amyloid β ($A\beta_{1-42}$); ↑ BDNF	70
Glucose metabolism	Wistar rats (M)	No challenge	3–30 i.p.	4	↑ Insulin secretion; ↓ hyperglycemia	N/A	44
	Swiss mice (M)	Streptozotocin challenge	3 i.p.	2	↓ Hyperglycemia	N/A	55
	Swiss mice (M)	Streptozotocin challenge	1–3 i.p.	2	↓ Hyperglycemia	N/A	56
	C57BL/6J mice (M)	Streptozotocin challenge	60 Drinking water	4	↓ Hyperglycemia; ↓ pancreas apoptosis; ↑ insulin secretion	↓ JNK; ↓ Bax/Bcl-2; ↑ PDX-1	57
Lipid metabolism and liver function	C57BL/6J mice (M)	High-fat diet challenge	15–60 p.o.	8	↓ Body weight; ↓ hepatic steatosis	↓ TNF-α; ↓ IL-6; ↓ COX-2; ↓ JNK; ↓ PPARγ; ↓ C/EBPα; ↓ FAS; ↓ ALT and AST	60
	C57BL/6J mice (F)	Hepatic steatosis (alcohol)	4 Drinking water	4	↓ Hepatic triacylglycerols	↓ iNOS; ↓ 4-HNE protein adducts; ↓ TNF-α; ↓ PAI-1; ↓ CD11c	61
	C57BL/6J mice (M)	Methionine- and choline-deficient diet challenge	10–30 p.o.	4	↓ Hepatic lipid accumulation; ↓ lipid peroxidation; ↓ hepatic ballooning, steatosis, and inflammation	↓ SREBP-1c; ↑ Nrf2; ↑ AMPK; ↓ TNF-α; ↓ MCP-1; ↓ FAS; ↓ ALT and AST	59
	C57BL/6J mice (M)	Streptozotocin challenge	60 Drinking water	28	↓ Hepatic injury	↑ Glycogen; ↑ glycolysis genes (Gck, Pk, and Pfk); ↑ AMPK	48
Inflammation	Sprague-Dawley rats (M)	LPS challenge	20 p.o.	4	↑ Phagocytic activity; ↑ NO	↑ TNF-α; ↑ IFN-γ	39
	Swiss albino mice (M)	Restraint stress (conical polypropylene tubes)	2 p.o.	14	↑ Th1/Th2 homeostasis; ↑ lymphocyte proliferation and T cell population [cluster determinants 3 (θ), 4(θ), and 8(θ)]	↑ CD28 and CD80; ↓ CTLA-4; ↓ CD152; ↓ IL-10; ↑ IFN-γ; ↑ IL-2; ↑ IL-12	85
	Sprague-Dawley rats (M)	Arthritis (collagen)	8–32 p.o.	28	↓ Paw swelling; ↓ organ index of the thymus and spleen	↓ NF-κB; ↓ TNF-α; ↓ COX-2	34
	ICR mice (M)	Anaphylactic shock (compound 48/80)	20 p.o.	2	↓ Mortality rate; ↓ histamine levels in blood serum	N/A	86

ICR, Institute of Cancer Research; M, male; F, female; ↑, increase; ↓, decrease; p.o., Per os (oral administration); i.p., intraperitoneal injection; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BACE1, neuronal β-secretase 1; BDNF, brain-derived neurotrophic factor; CD11c, integrin α X chain protein; CD28, cluster of differentiation 28; CD80, cluster of differentiation 80; CD152, cluster of differentiation 152; C/EBPα, CCAAT/enhancer-binding protein α; FAS, fatty acid synthase; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; Keap1, kelch-like ECH-associated protein 1; MCP-1, monocyte chemoattractant protein 1; PAI-1, plasminogen activator inhibitor-1; PDX-1, pancreatic duodenal homeobox 1; PPARγ, peroxisome proliferator-activated receptor γ; SREBP-1, sterol regulatory element-binding protein 1; Th1/Th2, T helper cells 1/2.

regulation of apoptosis-related genes, including c-Jun N-terminal kinase (JNK), B cell lymphoma 2-associated X/B cell lymphoma 2 (Bax/Bcl-2) ratio, and pancreatic duodenal homeobox 1 (PDX-1).[57] In addition, as stated in the previous section, chicoric acid downregulates several proinflammatory cytokines and mediators and these metabolic inflammatory cytokines are related to impairment of glucose homeostasis,[58] indicating that chicoric acid might improve glucose homeostasis through regulating inflammatory responses, including those associated with regulators COX-2, mitogen-activated protein kinase, cAMP response element-binding protein, and NF-κB.[47,48]

CHICORIC ACID AND LIPID METABOLISM AND LIVER FUNCTION

Chicoric acid has been found to reduce high-fat diet-induced weight gain in mice.[59,60] This was, in part, through inhibition of peroxisome proliferator-activated receptor-γ and CCAAT/enhancer-binding protein α, two critical transcription factors in adipocyte differentiation and lipid accumulation, while increasing the secretion of adiponectin.[60] Similarly, a few studies suggested that chicoric acid protected the liver from high-fat- or alcohol-induced fat accumulation and hepatic steatosis.[59–61] The hepatoprotective effects of chicoric acid were suggested to be due, in part, to a decrease in the Bax/Bcl-2 ratio and inhibition of fatty acid synthase and proinflammatory cytokines, including TNF-α, IL-6, COX-2, and JNK in the liver.[59,60]

CHICORIC ACID AND BRAIN FUNCTION

There is a report that chicoric acid treatment ameliorated restraint stress-induced behavioral despair and depression in mice.[62] These neuroprotective effects of chicoric acid may result from its upregulation of neurotransmitters, including noradrenaline, dopamine, and 5-hydroxytryptamine, in the whole-brain region of mice.[62] Since restraint stress is an important factor contributing to disorders and behavioral changes (such as depression, memory loss, anxiety, and learning disability), the possible alleviation of restraint stress by chicoric acid suggests the potential application of chicoric acid for the abovementioned brain disorders.[62]

Others reported that chicoric acid protected neurons from memory impairment, amyloidogenesis, and hippocampus shrinkage induced by LPSs and D-galactose in mice.[1,27,28] They also found that chicoric acid inhibited the expression of amyloid β and its downstream enzyme, neuronal β-secretase 1, both of which are known factors contributing to disruption of neural connectivity and neuronal death.[63] Meanwhile, chicoric acid upregulated brain-derived neurotrophic factor, which is a canonical nerve growth factor supporting the survival of existing neurons and promoting the growth of new neurons and synapses.[64] Although limited, these findings suggest the potential protective activity of chicoric acid in controlling the pathogenesis of neurodegenerative diseases.

ANTIOXIDATIVE STRESS EFFECTS OF CHICORIC ACID

Oxidative stress is defined as the imbalance between generation of reactive oxygen species (ROS) and a physical ability of detoxification or damage restoration associated with ROS.[65] ROS could act as cellular messengers, but cause physical damage through disruption of normal cell signaling pathways.[66] Chicoric acid has been found to have a high oxygen radical scavenging capacity, reducing the ROS level and protecting cells from free radical-induced cytotoxicity.[28,49,67–70] Moreover, chicoric acid increased the generation of antioxidative enzymes that contribute to reduction of ROS levels, that is, glutathione, glutathione peroxidase, superoxide dismutase, chloramphenicol acetyl transferase, heme oxygenase, and NAD(P)H dehydrogenase, in various cells.[28,41,42,47,48,68,70–72]

The underlying mechanism of the antioxidative effects of chicoric acid is attributed to enhanced nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf-2) and the level of peroxisome proliferator-activated receptor-γ coactivator α (PGC-1α).[28,68,70] Activation of Nrf-2 and PGC-1α inhibits ROS-induced cytotoxicity by upregulation of antioxidant response-related genes and promotion of the mitochondrial antioxidant defense system, respectively.[73,74] Since oxidative stress is closely related to development of certain cancers and chronic diseases, all these findings suggest the potential future application of chicoric acid for oxidative stress-associated diseases.

OTHER BIOACTIVITIES OF CHICORIC ACID

Chicoric acid, at relatively higher concentrations (105–315 μM), has been reported to inhibit cancer cell growth through inhibiting cell proliferation, promoting cell apoptosis, and deactivating telomerase through upregulation of DNA fragmentation, cleaved caspase-9, and cleaved poly-(ADP-ribose) polymerase.[75]

Another study suggested that chicoric acid ameliorated ultraviolet A irradiation-induced dermal fibroblast senescence by inhibition of matrix metalloproteinase-3 activity.[76] As dermal fibroblast senescence is a hallmark of intrinsic and ultraviolet-mediated aging,[77] this indicates the potential role of chicoric acid in aging.

SUGGESTED MOLECULAR TARGETS OF CHICORIC ACID

As discussed in previous sections, chicoric acid modulates genes, transcription factors, growth factors, enzymes, and proteins involved in important cellular processes, such as virus infection, chemoresistance, inflammation, and glucose metabolism.[36,46,71,78] Among them, it is suggested that NF-κB and TNF-α are two major mediators of chicoric acid's activities.

NF-κB is a protein complex involved in cellular responses to stress, free radicals, heavy metals, and bacterial or viral infections through regulating DNA transcription, cytokine production, and cell survival.[31,32,79] It is known

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that the activity of NF-κB is directly suppressed by binding with the inhibitor of κB (IκB) in the cytoplasm.[79] In contrast, phosphorylation of IκB releases and activates NF-κB.[79] Chen *et al.*[71] reported that chicoric acid deactivates NF-κB by inhibiting phosphorylation of IκB, indicating that IκB may be a major regulator for chicoric acid-mediated inactivation of NF-κB.

Alternatively, NF-κB can be activated in combination with TNF-α.[31] Several studies reported that chicoric acid decreased TNF-α production,[34,41,60,61,70] which might be a contributing factor to reduced activation of NF-κB. Chicoric acid-related deregulations of NF-κB and TNF-α were shown to alleviate conditions such as autoimmune disorders, restraint stress, hepatic steatosis, and neuron damage[28–30,34,41,59–61,70] known to be involved in cellular inflammation and associated diseases.[28–30,34,41,58–60,69]

PHARMACOKINETIC STUDY OF CHICORIC ACID

Chicoric acid is known to have relatively low absorption in rats.[80] The oral administration of chicoric acid at 50 mg/kg body weight resulted in a peak plasma concentration of chicoric acid at 1.63 ± 0.25 mg/L after 4 h.[80] Chicoric acid was mainly distributed in the liver, lung, and kidney after oral administration for 3 h. Chicoric acid has a relatively long residence time and low body clearance, 18.58 ± 4.43 h and 2.80 ± 0.46 L/kg/h, respectively, in rats.[80] All these findings help in better understanding the bioavailability and fate of chicoric acid.

CONCLUSION

Prevention of early-stage chronic diseases by food bioactive compounds seems to be a promising strategy. Chicoric acid's multibioactivities suggest that it has great potential in treating a number of metabolic disorders, including inflammatory responses, impairment of energy homeostasis, brain dysfunction, and immune disorders. Even though there are an increasing number of studies reporting bioactivities of chicoric acid, there are still limitations to arrive at a concrete conclusion due to differences in models, doses, and treatment durations used, as well as lack of pharmacokinetic study, including metabolism, of chicoric acid in humans. Thus, the research on chicoric acid is considered to be at an early stage, and there are still many questions that need to be answered regarding its benefits to health. More studies are needed to guide the development of chicoric acid-based functional food products.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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